21ST CENTURY CURES: MODERNIZING CLINICAL TRIALS

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

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HOUSE OF REPRESENTATIVES

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C O N T E N T S

21ST CENTURY CURES: MODERNIZING CLINICAL TRIALS

WEDNESDAY, JULY 9, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:01 a.m., in room 2123, Rayburn House Office Building, Hon. Joseph R. Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Whitfield, Shimkus, Murphy, Blackburn, Gingrey, McMorris Rodgers, Lance, Cassidy, Guthrie, Griffith, Bilirakis, Ellmers, Barton, Upton (ex officio), Pallone, Capps, Green, Barrow, Castor, and Waxman (ex officio).

Staff present: Clay Alspach, Chief Counsel, Health; Gary Andres, Staff Director; Matt Bravo, Professional Staff Member; Leighton Brown, Press Assistant; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Chris Sarley, Policy Coordinator, Environment and the Economy; Heidi Stirrup, Policy Coordinator, Health; John Stone, Counsel, Health; Ziky Ababiya, Democratic Staff Assistant; Eric Flamm, Democratic FDA Detailee; Debbie Letter, Democratic Staff Assistant; Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor; Rachel Sher, Democratic Senior Counsel; and Matt Siegler, Democratic Counsel.

Mr. PITTS. Subcommittee will come to order.

Chair will recognize himself for an opening statement.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Part of the work of our 21st Century Cures Initiative is to identify existing roadblocks to speeding treatments and cures to patients. One of these barriers is the current clinical trial process. Among the regulatory and administrative burdens associated with clinical trials are the expanding cost and size. While it takes on average approximately 14 years and $2 billion to bring a new drug to the market, a large portion of that cost is spent in recruiting and retaining subjects for clinical trials. It is often difficult to identify potential participants due to a shortage of centralized registries, low awareness of the opportunity to participate in clinical trials,

low patient retention, and lack of engagement among community doctors and volunteers.

Widespread duplication of effort and cost also occurs because research is fragmented across hundreds of clinical research organizations, sites, and trials, and information regarding both the successes and failures of clinical trials is rarely shared among researchers.

Finally, in many cases, researchers have been slow to utilize technology such as electronic health records and Web-based platforms in their trials, which is also a barrier to greater collaboration and information sharing. This expensive and antiquated clinical trials model is simply not acceptable in the 21st century. We can and must do better because patients deserve better.

Researchers and physicians are going to have to strengthen the recruitment and retention of volunteers for their trials, adopt new technologies, and above all, collaborate to build efficient and effective clinical trials.

I would like to thank all of our witnesses for being here today. I look forward to hearing of their ideas.

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

Part of the work of our 21st Century Cures initiative is to identify existing roadblocks to speeding treatments and cures to patients. One of these barriers is the current clinical trial process.

Among the regulatory and administrative burdens associated with clinical trials are their expanding cost and size.

While it takes, on average, approximately 14 years and $2 billion to bring a new drug to the market, a large portion of that cost is spent in recruiting and retaining subjects for clinical trials.

It is often difficult to identify potential participants, due to a shortage of centralized registries, low awareness of the opportunity to participate in clinical trials, low patient retention and lack of engagement among community doctors and volunteers.

Widespread duplication of effort and cost also occurs because research is fragmented across hundreds of clinical research organizations, sites, and trials, and information regarding both the successes and failures of clinical trials is rarely shared among researchers.

Finally, in many cases, researchers have been slow to utilize technology, such as electronic health records and web-based platforms in their trials, which is also a barrier to greater collaboration and information sharing.

This expensive and antiquated clinical trials model is simply not acceptable in the 21st century. We can and must do better because patients deserve better.

Researchers and physicians are going to have to strengthen the recruitment and retention of volunteers for their trials, adopt new technologies, and, above all, collaborate to build efficient and effective clinical trials.

I would like to thank all of our witnesses for being here today, and I look forward to hearing their ideas.

Mr. PITTS. I yield the remainder of my time to Dr. Burgess, vice chairman of the subcommittee.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. BURGESS. Thank you, Mr. Chairman, for the time. And thanks to our panelists for being here this morning. Certainly look forward to a good and lively discussion.

In many ways, randomized clinical trial, this country has set the gold standard for clinical trials, the rigorous investigative approach that we require. It does not mean that you can't make changes nor that you should not make changes to keep up with emerging

science and new techniques in investigational review all the while keeping a close and careful eye on patient safety. Failure to adapt could see what was once considered to be the standard of excellence in regulation quickly look out of place and out of touch with the field to which it applies.

Evidence A, Exhibit A is personalized medicine and the ability of the human genome to play a role in that. We are approaching a time when treatments could be tailored for a person's specific genetic code. There is no way such a revolutionary approach to treatment could be evaluated in the same way as a single-molecule drug meant for large populations.

Mr. Chairman, I certainly appreciate the subcommittee asking the question, how can we build in more flexibility? How can we stimulate innovation into the trial process so that these cures, which are just over the horizon, can become the reality of therapies for our patients?

These changes must ultimately retain the integrity needed to ensure that the end product is safe and effective. We cannot be caught off guard and risk watching innovative therapies suffocate at the hands of a regulatory system that has not kept up or further cripple the regulatory system by the approval of products that inherently are unsafe.

I welcome the testimony of our witnesses today. I will yield back to the chairman.

Mr. PITTS. Chair thanks the gentleman.

Now recognize the ranking member of the subcommittee, Mr. Pallone, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts. Today we continue our work on the 21st Century Cures Initiative, and the input from these hearings is valuable to our discussion. One of the primary lessons we have learned thus far, and I expect we will continue to hear today, is that discovering cures and effective treatments is complicated and difficult. But in the end when medical advances reach patients, we must ensure that they are safe and effective. And so I welcome today's discussion on clinical trials, which is a foundation of our drug and device regulatory system as well as the challenges and opportunities there are for modernization of the system.

Clinical trials give researchers, drug, and device developers and doctors a way to translate scientific advances into treatments for patients. While not every trial is a success, with every trial more knowledge is gained about drugs and devices that can be used to aid in the development of a future drug.

I think we would all agree that NIH and FDA are world leaders. They have proven that they have the ability and authority to integrate the newest science into their policies and approaches. The NIH-supported Human Genome Project has opened up a world of potential new drug treatment. The ground-breaking public-private collaboration of the Lung Cancer Master Protocol, or Lung-MAP,

which we will hear about from our witnesses today, represents an innovative approach to clinical testing.

Meanwhile, just last year, three-quarters of the new drugs approved by FDA were approved in the U.S. before any other country.

But there is nothing wrong with always striving to be better. The clinical development phase is the longest and most expensive period of product development, so it is important that we explore new tools, standards, and approaches that can be taken to assess the performance of medical advances.

Throughout this initiative, the question remains how Congress can advance these goals. The effort is a worthy one. It has been a great way for members and the public to explore and understand the complexity of issues that goes into discovery, development, and delivery of medicine.

But I have to caution my colleagues that when it comes to science, too much or too little is a hard balancing act especially to dictate in statute. We can't be the science experts. The greatest role Congress can play is ensuring that our Federal agencies have the flexibility and resources to apply the best regulatory science available.

On Friday, the subcommittee will hold another and related hearing on the engagement of the patient perspective during the development process. And I am glad that FDA will appear before this subcommittee then to talk about a number of innovative approaches they are taking in their recent regulation of drugs and devices.

I think that, Mr. Chairman, I think it is an exciting time in science and there are some amazing stories to be told. But despite this progress, there is more that can be done. But again, these are complicated issues that I hope we will continue to examine very carefully.

I would like to yield my last 2 minutes to Congresswoman Capps.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you to my colleague for yielding me time, and I thank you, Chairman Pitts and Ranking Member Pallone, for holding this important hearing.

I appreciate that this subcommittee wants to take action on this issue. It is a large one. Questions: How do we design a more modern clinical trial? How do we include the right mix of participants so the data are meaningful? How do we ensure that the data analyses performed actually look at differences on gender and ethnicity? How could postmarket surveillance and future passive data monitoring help inform our current system?

These are just a few of the many critical questions, and I encourage the subcommittee to have additional hearings so that we can truly focus on the many issues under the umbrella of modernizing clinical trials.

This is an issue very near and dear to me. For almost 10 years, I have worked to improve clinical trials and especially those involving women and children. And we have made some progress in recent years, and this has been with the passage of FDASIA and my own National Pediatric Research Network Act.

But, as you all know, there is much more work to do. And so I thank you all for being here. And I look forward to your testimony. And that is all I have to say on—I could yield back to the ranking member or just yield to any of my colleagues. I will yield back.

Mr. PITTS. Chair thanks the gentlelady. Now recognize the chairman of full committee, Mr. Upton, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRED UPTON, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MICHIGAN

Mr. UPTON. Thank you, Mr. Chairman. You know, at our first 21st Century Cures roundtable we learned that there are treatments for only about 500 of the more than 7,000 known diseases that affect our Nation's patients. We have also heard about the increasing time and expenses involved in bringing new drugs and devices to market, and we learned that the costs and regs surrounding clinical trials are a primary contributor to this delay. This means that new treatments and cures cost more and they are getting to patients more slowly. That system is simply unsustainable.

So here in the U.S., it is incredibly complicated to navigate the processes involved in simply getting a trial up and running. Particularly for small companies. Overall, the size, duration, costs, failure rates are higher than ever. In some cases, trials are being moved overseas as a direct result of those challenges. This leaves patients in the U.S. waiting longer for cures and treatments, and it also takes those jobs away from folks here at home. Safety is always the top priority. And I know, I know that we can do better. We must work together to remove any needless administrative or operational burdens that do not benefit patients.

In addition, we would like to learn more about recent advances in technology and data collection that can help modernize our system, encourage better participation, and certainly allow for continued learning about the risks and benefits of new drugs and devices in the real world.

How can we take what we learn in the development and delivery phases and translate that back to new, innovative discovery in this cycle of cures? How can we leverage patient registries in innovative new protocols, like the Lung-MAP trial, as well as other collaborative efforts into more advances into molecular medicine? Electronic health records, increased data sharing, and patient-reported outcomes will undoubtedly play a critical role in this regard. Ultimately, it is going to accelerate and modernize the discovery, development, and delivery cycle.

So today's hearing is yet another opportunity to discuss what can we do to further our journey on the path to cures.

PREPARED STATEMENT OF HON. FRED UPTON

At our first 21st Century Cures roundtable, we learned that there are treatments for only 500 of the more than 7,000 known diseases affecting our Nation's patients. We have also heard about the increasing time and expense involved in bringing new drugs and devices to market. We've learned that the costs and regulations surrounding clinical trials are a primary contributor to this delay. This means new treatments and cures cost more and are getting to patients more slowly. This system is simply unsustainable.

Here in the U.S., it is incredibly complicated to navigate the processes involved in simply getting a trial up and running, particularly for small companies. Overall, the size, duration, costs, and failure rates are higher than ever. In some instances, trials are being moved overseas as a direct result of these challenges. This leaves patients in the United States waiting longer for cures and treatments and also takes good jobs away from folks here at home. Safety is always the top priority, and I believe we can safely do better; we must work together to remove any needless administrative or operational burdens that do not benefit patients.

In addition, we would like to learn more about recent advances in technology and data collection that can help modernize our system, encourage better participation, and allow for continued learning about the risks and benefits of new drugs and devices in the real world. How can we take what we learn in the development and delivery phases and translate that back to new, more innovative discovery in the cycle of cures? How can we leverage patient registries and innovative new protocols like the Lung-MAP Trial, as well as other collaborative efforts, into more advances in molecular medicine?

Electronic health records, increased data sharing, and patient-reported outcomes will undoubtedly play a critical role in this regard. Ultimately, this will accelerate and modernize the discovery, development, and delivery cycle.

Today's hearing is another important opportunity to discuss what can be done to further our journey on the path to cures.

Mr. UPTON. And I would yield to Marsha Blackburn.

OPENING STATEMENT OF HON. MARSHA BLACKBURN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TENNESSEE

Mrs. BLACKBURN. Thank you, Mr. Chairman. And I want to welcome all of you. We appreciate that you are here as we look at modernizing clinical trials.

Federal law requires that medications proposed for human use be safe and efficacious. That means that our constituents can expect medicines to do exactly what they are advertised to do and that any side effects are going to be clear and apparent to these patients. And the major mechanism by which medicines are found to be safe and efficacious are the phase III clinical trials, which test the drugs against placebos and the other known treatments. We all appreciate that process. And what we want to do is look at how we are going to be able to modernize this process as we go through the trials with large groups of people, sometimes thousands, with the intent of finding the side effects that could harm even a small percentage of individuals.

The large groups also make the statistics work, giving greater assurance that the drug does do what it is purported to do. The importance of the phase III trials is reflected in the statutory language in the FD&C Act. The FDA generally requires drug companies to sponsor at least two such clinical trials for a new drug. I would be interested to hear from you: Do you think that is enough? Too much? How should that be changed? Also, the phase III trials are the gold standard for drug approval. They have their limitations. How would you address those limitations? Today we are going to look at that gold standard and the limitations of the phase III trials. And hear of your base to build upon what we have learned in order to speed safe and efficacious treatments to patients.

I thank you for your time, and I yield back to the chairman.

Mr. UPTON. Yield back.

Mr. PITTS. Chair thanks the gentlelady.

Now recognize the ranking member of the full committee, Mr. Waxman, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman.

The topic of this hearing is an important one. Clinical trials are the bedrock of modern medical product development. We rely on clinical trials to demonstrate that our drugs and devices are safe and effective, and we rely on the willingness of people to volunteer to participate in these trials. So of course, we want to ensure that clinical trials are conducted using the most modern tools and technology that science has to offer.

We also need to ensure that clinical trials are conducted in the most efficient manner possible. That is why NIH and FDA have been leaders in working with academia and industry to identify areas in which the clinical trial process can be improved. These improvements could include encouraging the use of centralized institutional review boards, developing standards for harmonizing the collection and exchange of data, and maintenance of patient registries to facilitate the recruitment of patients for clinical trials. And I look forward to hearing more today about such efforts.

How Congress can help advance these goals is a complicated question. The 21st Century Cures Initiative is useful because it is shining a light on some important issues surrounding how drugs and devices are developed and ultimately delivered to patients.

There are some clear areas where Congress could legislate. We should ensure that both FDA and NIH have the resources they need to remain the gold standard in observing clinical trials. But when it comes to legislating how clinical trials are conducted, we need to proceed with great caution. Congress should not be in the business of dictating the kind or level of evidence needed to permit drugs and devices to go on to the market. That decision is solely the task of the scientific experts at the Food and Drug Administration. We should not force FDA to prematurely accept novel technologies. Our job should be to ensure that FDA has the regulatory authority needed to make use of the latest scientific advances.

When FDA testifies on Friday, the agency can tell us about how it is applying novel approaches to clinical trials in their regulation of drugs and devices. I would also like to know whether the agency believes it has the authority necessary to adopt new approaches and whether other new statutory powers are necessary. In this area, we need to be careful not to try to fix things that are not broken. That could harm a system that is already working. We should create policies that foster scientific advances. But we should not enact regulatory policies based on how far we wish scientific development has progressed.

I thank you, Mr. Chairman. And I am willing to yield my time to anyone who might want it. Otherwise, I yield it back.

Mr. PITTS. Chair thanks the gentleman. That concludes the opening oral statements of the members. All members' written opening statements will be made a part of the record.

We have one panel today with seven witnesses. And I will introduce them in the order that they present their testimony.

First, Dr. Robert Meyer, Director, Virginia Center for Translational and Regulatory Sciences, University of Virginia School of Medicine; Dr. Aaron Kesselheim, Assistant Professor of Medicine, Harvard Medical School, Director, Program on Regulation, Therapeutics, and Law Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital; Mr. Bill Murray, President and CEO, Medical Device Innovation Consortium; Dr. Jay Siegel, Chief Biotechnology Officer and Head Scientific Strategy and Policy, Johnson & Johnson; Dr. Roy Herbst, Chief of Medical Oncology, Yale Cancer Center; Dr. Sundeep Khosla, Director, Center for Clinical and Translational Science, Mayo Clinic; and Ms. Paula Brown Stafford, President, Clinical Development, Quintiles.

Thank you for coming. You will each have 5 minutes to summarize your testimony. And your written testimony will be placed in the record.

Dr. Meyer, we will start with you. You are recognized for 5 minutes for an opening statement.

STATEMENTS OF ROBERT J. MEYER, DIRECTOR, VIRGINIA CENTER FOR TRANSLATIONAL AND REGULATORY SCIENCES, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE; AARON S. KESSELHEIM, ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, AND DIRECTOR, PROGRAM ON REGULATION, THERAPEUTICS, AND LAW (PORTAL), DIVISION OF PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS, BRIGHAM AND WOMEN'S HOSPITAL; BILL MURRAY, PRESIDENT AND CEO, MEDICAL DEVICE INNOVATION CONSORTIUM; JAY P. SIEGEL, CHIEF BIOTECHNOLOGY OFFICER AND HEAD OF SCIENTIFIC STRATEGY AND POLICY, JOHNSON & JOHNSON; ROY S. HERBST, ENSIGN PROFESSOR OF MEDICINE AND CHIEF OF MEDICAL ONCOLOGY AND ASSOCIATE DIRECTOR FOR TRANSLATIONAL RESEARCH, YALE CANCER CENTER; SUNDEEP KHOSLA, DEAN FOR CLINICAL AND TRANSLATIONAL SCIENCE, MAYO CLINIC; AND PAULA BROWN STAFFORD, PRESIDENT, CLINICAL DEVELOPMENT, QUINTILES

STATEMENT OF ROBERT J. MEYER

Mr. MEYER. Thank you, Chairman Pitts, Ranking Member Pallone, and members of the committee.

As stated, I am Dr. Bob Meyer, and I direct the Center for Translational and Regulatory Sciences at the University of Virginia. I am, by background, a pulmonary physician, and previously held senior leadership roles within the Center For Drug Evaluation and Research at FDA as well as in Merck Research Labs, where I headed global regulatory strategy, policy, and drug safety, and was a key participant in their late-staged development committee, which the committee that was responsible for the oversight of late-stage development trials within Merck's portfolio.

While I am now academics, I think I have a very real and tangible experience with regard to clinical trials challenges from both

a regulatory and industry perspective, and, therefore, I am pleased to be here today.

Modern clinical development programs are large, complex, and usually global in scope and in conduct. And are increasingly expensive to conduct.

Compounding this rising cost is the fact that the success rate for drugs entering into phase III to achieve final regulatory approval is falling, and the rate is now approximating only 50 percent.

There are myriad of drivers that have contributed to the growth and larger, longer, and more complex phase III trials, including regulatory demands. However, I think it is important to focus beyond FDA in the considerations on how to address some of these issues. And let me speak to a few of these. I would say that I am going to keep this statement short because I believe many of these points will be more eloquently made by others on the panel.

The first consideration that I would raise is better trial standardization. In phase III programs, there is a large amount of time expended getting from study concept to the first patient enrolled. And the sponsors usually recapitulate these efforts for each program as if each one is a wholly new effort. This then raises two important points for consideration.

First is the enhanced development of effective, lasting, durable clinical trial networks. Networks can bring efficiencies such as having identified patient populations and qualified and ready clinical sites that can reduce some of the time and effort spent in study startups. There are efforts towards clinical trial network development in certain disease areas, such as the National Cancer Trials Network. However, this model is not as widespread as it should be or could be, particularly taking into account the varied areas of unmet medical needs.

Second concept is the development of master protocols. Such master protocols could serve as the basis for use by different investigators or sponsors with minimal modification, save for the details of the particular test product.

An added benefit of wider use of shared standardized protocols is this would also enhance the ability to interpret these trials in cross-study comparisons to assess relative efficacy, safety, or other attributes considered important to physicians, patients, and payers, since the patient populations and end points would be highly similar.

Another consideration is the increasing complexity and design of modern clinical trials. This trend to increasing complexity is reflective of the fact that modern trials are designed to address an increasing number of demands from differing regulatory demands across the globe, differing payer expectations, differing market claims sought, the use of new exploratory science or end points within the trials, and interest and input of key opinion leaders who participate in the design of the trials.

I believe sponsors could benefit from further concerted efforts to simplify trials by using multidisciplinary groups within the company and outside the companies tasked to maximize the value of the trial while minimizing the complexity and cost.

I also believe FDA could aid in this effort in the end of phase II advice. But to do so they would need to recruit more experienced

industry personnel with practical clinical trial design in the operations experience because this kind of expertise is rare within the agency.

An additional consideration in reducing clinical trial expenditures is moving further away from the paradigm of face-to-face clinical evaluations as the gold standard for patient evaluation. There is an increasingly sophisticated ability to assess patient status and accrue sophisticated clinical data via new technologies.

So in light of the other expertise on the panel, let me close by saying these efforts to think about how we can modernize clinical trials are critically important. However, I think that the evaluation of safety and efficacy is a critical safeguard to patients within the U.S. And I think the way that this currently is done within the U.S. is, in fact, the gold standard not only within the U.S. but across the globe. And I would urge that the increasing daunting costs and the challenges of medical clinical trials are addressed in a way that preserves the assurance that drugs on the market are safe and effective.

We must seek a way to deploy practice, into practice the efficient modern clinical trials, incorporate new technologies and science where appropriate and validated while maintaining the integrity of the regulatory progress.

Thank you for this opportunity to participate in the hearing.

[The prepared statement of Mr. Meyer follows:]

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Statement of

Robert J. Meyer, MD[1]

Director of the Virginia Center for Translational and Regulatory Sciences

Associate Professor of Public Health Sciences,

University of Virginia, School of Medicine

Charlottesville, Virginia

Before the House of Representatives

Subcommittee on Health, of the

Committee on Energy and Commerce

Hearing: 21st Century Cures: Modernizing Clinical Trials

July 9th, 2014

[1]Note: Dr. Meyer is participating in this hearing per invitation and on his own behalf; the views expressed in this statement are not necessarily those of the University of Virginia or of the Commonwealth of Virginia

Chairman Pitts, Ranking Member Pallone and Members of the Committee. I am Dr. Bob Meyer, Director of the Virginia Center for Translational and Regulatory Sciences at the University of Virginia, School of Medicine, where I also serve as an Associate Professor of Public Health Sciences. I am a pulmonary physician by training who, previous to my move to Virginia, has held senior leadership positions within the Center for Drug Evaluation and Research at FDA, as well as at Merck & Co., Inc. At Merck Research Labs, I was head of Global Regulatory Strategy, Policy and Drug Safety and therefore was a key participant in their Late Stage Development Committee, the committee responsible for oversight of the planning and conduct of clinical trials in support of Merck's portfolio of new medicines and vaccines. I am very cognizant of the challenges of clinical trials both from a regulatory and industry perspective. Therefore, I am pleased to be here today to share my perspective on the topic of modernizing clinical trials, as this is an important and integral part of the broader considerations on providing for a robust therapeutic development ecosystem in the United States, one that both provides for US patients having access to important new, effective medical advances, as well as a healthy biotechnology industrial sector that assures employment to a large, sophisticated workforce.

It is well documented that one of the major categories of expenditure in developing a new therapeutic is the expense of conducting the necessary late-stage (or phase 3) clinical trials, which are intended to address the regulatory expectations in the US and beyond. Modern clinical development programs are generally large, complex and often global in both scope and conduct. As a result, these programs are increasingly expensive. In fact, the proportion of total clinical development expenditure that is devoted to phase 3 trials alone is roughly 75-95% of the total spend, depending on the disease category.[i] Compounding this is the fact that the success rate for drugs entering into phase 3 in achieving final approval is falling, with the rate now approximating 50%. This means that not only is the conduct of phase 3 trials for a new drug a large investment, but these expenditures are sometimes for naught. This adds to the phase 3 clinical trials expenditures per successful drug.

There are a number of drivers that have contributed to the growth in larger, longer and more complex phase 3 clinical trials, including regulatory demands. However, I think it important to not solely focus on this issue as being a consequence of regulatory requirements, as these drivers are multidimensional.

Let me make an important point first and foremost - some have proposed that one means of addressing both the costs and failures of phase 3 trials is to shift regulatory decision making earlier, leaving "confirmatory" efforts to the post-approval setting. I would caution against this. The fact that many products fail in phase 3 reflects the realities of science as much as any issue correctable in the design and conduct of trials. Indeed, since roughly half of phase 3 failures can be ascribed to failures in proving effectiveness[ii], this signals a clear cautionary note for lessening the demands during phase 3. Additionally, these proposals often cite the desire to use real world data to finally confirm effectiveness. I do not believe that current observational methods allow for the kind of rigorous assessment of efficacy that patients and their physicians deserve and payers demand, even given the very real promise of big data and the systematic research use of electronic health records.

What then are some of the considerations that I would recommend be taken into account in the discussion of how to effectively modernize clinical trials?

1. The first considerations relate to opportunities in standardization. In phase 3 programs, there is a large amount of time expended getting from study concept to first patient enrolled. The effort and time spent by sponsors in all aspects of study start-up are considerable (time from trial concept to final protocol, to then identifying study sites capable of rigorously conducting the research while providing for a sufficient patient-base, and then in the mechanics of training the study site in the particulars of the study and getting the requisite Ethics Committee approval). All this is effort occurs prior to even one patient being enrolled. And sponsors go through this time and

again, as de novo efforts, for each program. These efforts represent systemic inefficiencies which in turn raise two important points worthy of consideration.

a. The first is the enhanced development of effective, durable clinical trials networks that have the potential to obviate the need for approaching each new trial as a de novo effort. Networks can have identified patient populations, clinic sites and ongoing research efforts that would help reduce time and efforts spent in study start up. There are efforts towards clinical trials network development in certain disease areas (a good example is the 2014 initiative from the National Cancer Institute in its National Cancer Trials Network, undertaken in response to the Institute of Medicine's call for such a network to reinvigorate innovation in cancer therapeutics).[iii] However, while there are instances of successes in trials network development, this model is not as wide spread as it could or arguably should be, particularly taking into account the varied areas of unmet medical needs (e.g., pediatric drug development). While one might regard Contract Research Organizations (or CRO's) as perhaps being tantamount to trial networks given their focus on operational efficiencies, the competitive nature of the many clients they serve is an impediment to the CRO's achieving anything close to the kind of efficiencies possible in networks. The issue of competition means that the broader development of clinical trials networks would likely not come from industry or CROs alone, but would entail Public-Private partnerships, with the appropriate agencies of the federal government partnering with industry and academia in a dedicated effort to set them up and maintain and hone them over time.

b. A second concept that is not at all exclusive of the idea of broader trial networks is that of the development of master protocols. Such master protocols could serve as the basis for use by different investigators or sponsors with minimal modification (save for the details of the particular test product). When faced with important diseases being targeted by

multiple sponsors simultaneously, each interested in developing new therapeutics for those diseases, there could be a significant opportunity for developing such master protocols. For instance, clinical trials for the treatments of melanoma – a deadly form of skin cancer – are burgeoning right now. But the trials differ in details of design which leads to inefficiencies for the sponsors, the sites and in potential patient recruitment. The benefits of having well-honed standardized protocols to inform the protocols for trials undertaken within a targeted disease area (particularly where networks have been developed) could certainly enhance the efficiencies in the planning and conduct of these trials. Use of master protocols could also enhance the ability to interpret these trials in cross-study comparisons to assess relative efficacy, safety or other attributes considered important to physicians, patients and payers, since the patient populations and endpoints would be highly similar. As with networks, however, this again entails broader efforts beyond the biotechnology industry, as protocol development within a company is clearly viewed as competitive and proprietary.

2. A second consideration when it comes to the cost of phase 3 trials is the increasing complexity in design of modern clinical trials. For instance, a recent study out of Tufts showed that the number of endpoints and procedures in clinical studies has gone up by more than 60% from 2002 to 2012. At the same time, this study showed that a minority of the procedures, endpoints and related trial costs in phase 3 trials are driven by regulatory requirements. Non-core elements of these trials were estimated in this study to total in the range of 4-6 billion dollars of aggregate spend across the industry.[iv] This trend to increasing complexity is reflective of the fact that modern trials are designed to address an increasing number of demands (e.g., differing regulatory demands across regions, differing payer expectations, addressing marketing claims, new exploratory science/endpoints, interests/input of key opinion leaders, etc.). While some

of the increase in complexity may be an unavoidable cost of modern drug development, some of this is self-inflicted and can be addressed by sponsors through purposeful efforts focused on designing efficient, focused and feasible trials. While interdisciplinary oversight committees aimed at achieving simplified, efficient trial designs are being implemented by some sponsors, I believe this is still not the norm. I further think that such efforts should be encouraged by FDA during end-of-phase 2 discussions with sponsors. I should point out, however, that while FDA has much expertise in review and regulatory oversight of clinical trials, there are very few people within the FDA who have had practical experience in clinical trials planning and operations. Therefore, while it would be advantageous to have FDA take this on as a part of their mission, very few within the Agency truly understand in detail the demands and drivers of trial planning and conduct with the kind of granularity necessary to serve as effective advisors and advocates for decreasing complexities of clinical trials. In other words, were FDA to take on this role more actively, they would need to recruit and/or develop the requisite expertise.

3. A third consideration in reducing clinical trial expenditures is moving further away from the past paradigm of regarding face-to-face clinical evaluations as the gold standard of patient evaluation. There is an increasingly sophisticated ability to assess patient status and to accrue sophisticated clinical data via new technologies, technologies that integrate accurate patient-based assessments with the ability to collect and transmit real-time data. Yet, these technologies have yet to reach full fruition as fundamental elements of phase 3 trials. There is a tremendous opportunity to incorporate into modern trial designs an approach that replaces some or in some instances even all patient visits to investigative sites with the use of "at home" assessments. For this to be fully implemented, FDA itself will need to continue to participate in discussions on important issues such as device approval status, measurement properties (e.g., accuracy and precision), data

integrity given the real time accrual of data and lack of written source records, and means to ensure patient privacy. While some elements of patient-based electronic data generation and capture have become routine, these technologies and approaches are ripe for broader use and doing so could lead not only to more efficient trial designs, but arguably more accurate data. For instance, an increase in the frequency of assessments can lead to better precision in estimating treatment effects. All of these enhancements could replace patient evaluation visits and thereby save clinical expenditures and alleviate patient burden (perhaps then enhancing recruitment).

4. Two other considerations that have been much discussed and oft times debated in this vein include increasing the regulatory acceptance of adaptive trials, as well as the need for efforts to spur the development of new means endpoints (such as new surrogate measures and/or new patient-reported outcome tools). Let me briefly touch on both.

    a. While adaptive designs are increasingly common in drug development, they have been most commonly implemented in the design of earlier phase studies, where the scientific "risks" are borne more by the sponsors than the public and/or regulators. There are fewer successful examples of effective use in late phase 2 and phase 3. I believe this reflects the reality that the pluses of adaption (speed, efficiencies) are traded off with complexities in design, conduct and interpretation. One especially notable hope for adaptive designs is the idea of eliminating development "white space" through the use of what is termed a seamless phase 2-3 trial – trials where a successful phase 2 study transitions automatically into phase 3. While this sounds attractive, this kind of adaptive trial raises many significant issues – not the least of which is the loss of the ability to conduct a true "learn and confirm" development paradigm, which is the very

heart of cogent drug development. If there is any message in the rising failure rate of phase 3 trials, I think it is that the increasingly parallel drug trials paradigm (rather than the serial learn-and-confirm model) does not allow for enough careful thought of past results to properly inform future designs.

b. On the topic of new endpoints, there is little debate about the need for such – particularly in areas of unmet medical need. For many areas of unmet need, the uncertainties on regulatory pathway, including the absence of acceptable endpoints, are substantial impediments to develop of new therapeutics. Yet developing and validating new endpoints, such as validated surrogate assessments and/or patient-reported outcome instruments is complex and too time consuming. While developing new surrogate endpoints and patient-reported outcome instruments to the point of regulatory validation is broadly supported, an important question is how to best drive this process scientifically and practically. While the FDA must be involved in these efforts, FDA is not best equipped to drive the efforts from either the perspective of having the resources to do so or the requisite expertise. While Public-Private partnerships can succeed, a recent experience with a specific program – the EXACT-PRO initiative[v] – demonstrates how long and arduous this can be (the EXACT-PRO initiative began in 2004 during my FDA tenure but only resulted in the FDA regulatory guidance declaring it sufficiently validated nearly a decade later[vi]). As with many of these issues, a more concerted, broader effort would be needed to address this need systemically with a goal towards the timely development of endpoints in targeted areas with the greatest need for such.

In closing, let me say that I believe that efforts to modernize clinical trials are critically important as a part of the broader discussions on how to advancing innovative therapeutics. I further believe there is much that can be done to

achieve better efficiencies in drug development without undermining the traditional paradigm of requiring "substantial evidence of effectiveness" prior to regulatory approval. The thorough evaluation of safety and efficacy is critical safeguard to patients within the US since it assures that new therapies are convincingly shown to have a favorable risk-benefit profile via well-conducted randomized controlled trials. I would also add that the current regulatory/development system, inefficient as it may be, still leads to innovative drugs being available first to the US market more often than any other market globally[vii] and these FDA approval decisions are regarded as a reference standard to many regulators across the globe. At the same time, the increasingly daunting costs faced by sponsors in conducting phase 3 trials and the impact on the sustainability of therapeutic development is undeniable. Therefore, a systematic and systemic effort undertaken in collaborations across government, industry and the public sector is needed, all with the goal to apply best thinking and practice to the achievement of efficient, modern clinical trials.

Thank you for this opportunity to participate in this hearing.

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[i] Roy, Avik Project FDA Report: Stifling New Cures: The True Cost of Lengthy Clinical Drug Trials. Manhattan Institute for Policy Research, #5: April 2012

ii Hay, et al. Clinical development success rates for investigational drugs, *Nature Biotechnology 2014* 32, pp 40–51

[iii] A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program; http://iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx

[iv] Getz, K "Improving Protocol Design Feasibility to Drive Drug Development Economics and Performance." Int. J of Environ. Res. Public Health, 2014, 11: 5069-80

[v] http://www.exactproinitiative.com/

[vi] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM380961.pdf

[vii] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm

Mr. PITTS. Chair thanks the gentleman.

Now recognizes Dr. Kesselheim for 5 minutes for an opening statement.

STATEMENT OF AARON S. KESSELHEIM

Mr. KESSELHEIM. Thanks very much, Subcommittee Chairman Pitts, Ranking Member Pallone, and members. I am Aaron Kesselheim. I am a physician, lawyer, and health policy researcher at Harvard Medical School. And it is an honor to have the opportunity to share my thoughts with you about modernizing clinical trials and helping expedite access to new prescription drugs and medical devices.

About 50 years ago, Congress decided that new therapeutics should have their efficacy and safety demonstrated before they could be widely used by patients. This wasn't a capricious attempt by legislators to prevent patients from getting the treatments they need, but a rational response by public servants to major public health tragedies caused by the lack of such proof.

When Congress originally gave FDA this power, it did not require any particular kind of test. All that is statutorily required is that manufacturers provide substantial evidence that the drug will have the effect it purports to have, with "substantial evidence" being defined as adequate and well controlled investigation.

Unfortunately, some manufacturers will not subject their healthcare products to studies meeting even these minimal criteria without the FDA standard-setting authority. Take a look at the dietary supplement market if you don't believe me. Indeed, in the decade after these regulations were put in place, FDA regulators removed hundreds of drugs that failed to show sufficient evidence of effectiveness upon clinical study.

To meet these criteria, the FDA prefers randomized trials with blinded assignment and placebo or active comparator controls. And so does the world scientific community. It's worth recalling that a randomized control trial was once an innovation. The basic requirements for conducting these trials became recognized and codified slowly over the course of the 20th century after decades of debate and consideration, leading to consensus about their most important characteristics.

At the same time, subjecting a new product to a formal, randomized control trial or testing a hard clinical end point could delay availability of promising products to some patients in life-threatening circumstances. Fortunately, as currently written, the law gives the FDA flexibility to accept data short of traditional randomized trials to approve therapeutics for important unmet needs or where randomization may be ethically or practically impossible.

These products may get assigned by the FDA to special fast track, or accelerated approval pathways, or receive congressionally authorized designations that signal their special status, like "orphan drug" or "breakthrough drug" or "humanitarian device."

Studies conducted by myself and others show that products with these designations are often provided with expedited review by the FDA, many receiving approval based on uncontrolled studies and small populations.

Expedited approval pathways and special designations are common at the FDA. In 2012, 26 of the 39 new drugs approved qualified for at least one such program. And the FDA now approves about two-thirds of new drugs earlier than its counterparts in Europe.

When medical products are approved without being subject to randomized trials testing real clinical endpoints, it puts patients at increased risk. Medical history is littered with drugs and devices approved on the basis of unvalidated biomarkers that have their indications later withdrawn or altered, or cancer drugs, originally approved on uncontrolled trial later demonstrated in better controlled trials finally conducted a decade later to actually increase the risk of death.

In 2012, the multi-drug resistant tuberculosis drug, bedaquiline, was approved on the basis of two short-term trials testing about 200 patients after being granted accelerated approval status, fast track, orphan drug status, and priority review. In these studies, the drug was only shown to improve the questionable surrogate endpoint of converting sputum from tuberculosis positive to negative. But two-and-a-half times as many patients died from tuberculosis in the bedaquiline group than the control group. Patients with tuberculosis want to be cured, they don't want to die with cleaner sputum.

How do patients and individual physicians now make sound benefit/risk determinations about this drug or others like it in the absence of more conclusive scientific data?

The prospect of approving more drugs on the basis of trial designs that diverge from traditional randomized trials also puts pressure on the timely conduct of confirmatory clinical trials and postapproval surveillance systems. But studies show that manufacturers' commitments to continue studying their products after approval may be delayed or incomplete.

Once a drug is FDA approved for a certain indication, convincing patients to subject themselves to further randomized trials of the drug for that indication can be challenging because patients can receive the drug outside the trial. It is no wonder that the FDA gave the makers of bedaquiline until 2022 to complete confirmatory trials of that drug's effectiveness in tuberculosis.

In summary, the prospect that researchers can design new ways of conducting clinical trials of investigational drugs is exciting. And I hope that the best of these truncated designs are proven to provide the same level of confidence as standard randomized controlled trials.

But the FDA already has the flexibility in its laws and regulations to accept innovative study designs short of randomized trials and validated biomarkers that can accelerate the testing of truly important new drugs and medical devices.

The fast track process reduced clinical development time of a new drug from 8.9 to 6.2 years; accelerated approval drugs have an average of just 4.2 years of development.

And the FDA already exercises its flexibility to a remarkable extent. If regulators and others in the medical community are still skeptical about certain biomarkers and clinical trial designs, it is probably because the science supporting them is still in its infancy;

in which case, forcing approval of the drugs or devices to which they are applied would be dangerous and counterproductive for the very patients we are all trying to help. Thank you.

[The prepared statement of Mr. Kesselheim follows:]

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21ST CENTURY CURES: MODERNIZING CLINICAL TRIALS

Testimony of:

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United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health
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Summary of major points

- Congress made the decision that new drugs and high risk medical devices should have their efficacy and safety demonstrated before they could be widely used by patients as a rational response to major public health tragedies caused by the lack of such proof.
- The FDA and Congress have initiated numerous flexibilities to allow the FDA to approve important new drugs on the basis of studies less rigorous than traditional randomized clinical trials testing validated clinical endpoints. These flexibilities shorten premarket testing and regulatory review times and are often employed by the FDA.
- Although the FDA was once considered by some to approve drugs too slowly, drug approvals since 2000 have been quicker in the United States than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency
- When drugs and high risk medical devices are approved without being subject to rigorous testing, it puts patients at risk. Post-approval study of these drugs is difficult and can be time-consuming. Post-approval surveillance innovations like registries and the Sentinel system are promising but still in active development.

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Subcommittee on Health Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham & Women's Hospital in Boston and an Assistant Professor of Medicine at Harvard Medical School. I lead the Program On Regulation, Therapeutics, And Law, an interdisciplinary research core that uses empirical approaches to study intersections between laws and regulations and the development, utilization, and affordability of therapeutics. It is an honor to have the opportunity to share my thoughts with you about modernizing clinical trials and helping expedite access to new prescription drugs and medical devices.

About 50 years ago, Congress made the decision that new drugs should have their efficacy and safety demonstrated before they could be widely used by patients. Congress extended this requirement to a small subset of the highest risk medical devices about a decade later. This wasn't a capricious attempt by legislators to prevent patients from getting the treatments they need, but a rational response by public servants to major public health tragedies caused by the lack of such proof, such as when patients died after taking products with poisonous constituents (sulfanilamide elixir), gave birth to babies with devastating congenital anomalies (thalidomide), or used contraceptive devices that caused bacterial sepsis (Dalkon Shield). In a letter to Congress at the time, President Kennedy highlighted the importance of rigorous testing of new drugs, stating that "[O]ver 20 percent of the new drugs listed since 1956 in the publication New and Non-Official Drugs were found, *upon being tested*, to be incapable of

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sustaining one or more of their sponsor's claims regarding their therapeutic effect" (emphasis added).[1]

When Congress originally gave FDA the power to require new drugs and high risk medical devices to be tested before they could be prescribed to patients, it is worth noting that Congress did not specifically require any particular kind of test. All that is required is that manufacturers provide "substantial evidence that the drug will have the effect it purports or is represented to have," with substantial evidence being defined as "adequate and well-controlled investigations, including clinical investigations." In regulations, the FDA has defined "adequate and well-controlled" as studies having a clear statement of purpose, that permit valid comparison of an experimental and a control group, employ suitable methods to assign study and control groups and otherwise minimize bias, using clear, reliable methods to analyze the study results. These aren't exactly controversial features of a clinical trial. Unfortunately, without the FDA authorized as a gatekeeper in this market, manufacturers of most new drugs and medical devices at the time did not subject their drugs to studies meeting even these minimal criteria, and in the decade after these regulations were first put in place, FDA regulators removed literally hundreds of widely used drugs because they failed to show sufficient evidence of effectiveness upon clinical study.

Generally, the FDA prefers randomized controlled trials, blinded and placebo- or active comparator-controlled, to meet these basic criteria. It is worth recalling that a randomized trial was once an innovation. The requirements for an acceptable randomized clinical trial became recognized and codified slowly over the course of the twentieth century, after decades of debate and consideration leading to consensus about their most important characteristics.[2] But the FDA

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has also recognized that subjecting a new product to rigorous study before approval could prevent timely availability of these products to some patients in life-threatening circumstances. In response, starting informally in the 1970s and spurred on by AIDS activists in the 1980s, the FDA designed the fast track and accelerated approval programs that explicitly permitted truncated pre-market study of drugs and devices for patients with serious or life-threatening conditions. Congress has similarly created special designations for certain drugs and medical devices—using terms such as priority review, orphan drugs, humanitarian devices, and most recently breakthrough drugs—to signal their importance to the FDA. Drugs with these designations are often granted flexibilities in their premarket testing and provided with expedited review by the FDA, and many ultimately receive approval based on uncontrolled studies in small populations rather than randomized trials testing clinical endpoints. As a result, these drugs and devices naturally spend far less time in pre-market development. Fast track, for example, reduced the average clinical development time for a new drug from 8.9 to 6.2 years, whereas drugs benefiting from accelerated approval averaged just 4.2 years. NDA review times have also decreased dramatically, from more than 30 months in the 1980s to 14.5 months by 1997 and to 9.9 months for applications received in 2011.[3] We did a study and found that cancer drugs tagged with the "orphan drug" label were overwhelmingly more likely to be tested in methodologically weaker assessments as parts of trials that were more likely to be non-randomized, unblinded, single-arm trials, and/or considered only intermediate surrogate endpoints such as "disease response" rather than survival.[4] These days, expedited approval programs and special designations have become common at the FDA—in 2012, 26 of the 39 new drugs approved qualified for at least one of these expedited programs. Although the FDA was

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once considered by some to approve drugs too slowly, drug approvals since 2000 have been quicker in the US than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency.[5]

When drugs and high risk medical devices are approved without being subject to rigorous testing, it puts patients at risk. More drugs being approved on the basis of uncertain data will inevitably lead to more drugs being withdrawn from the market after showing safety problems, or weaker-than-expected effectiveness in widespread clinical use. In our study of approved orphan and non-orphan cancer drugs, we found that serious adverse drug events were significantly more likely to occur in orphan drug pivotal trials, as compared with more rigorous pivotal trials of non-orphan drugs. It also creates a conundrum for patients and physicians. What are physicians supposed to recommend to their patients if the FDA approves a product based on a new clinical trial design that has not yet been confirmed to provide valid data or based on an unvalidated biomarker instead of a real clinical endpoint? Take the case of bedaquiline, a drug for multidrug-resistant tuberculosis approved in 2012 after being granted accelerated approval status, fast track, orphan drug status, and priority review on the way to approval based on two short-term trials testing about 200 patients. In these studies, which were randomized and placebo-controlled, the drug showed efficacy on the questionable surrogate endpoint of converting sputum from *M. tuberculosis* positive to negative. But 2.5 times as many people died from tuberculosis, and 5 times as many people died overall, in the bedaquiline group than in the control group.[6] Patients with tuberculosis want to be cured – they don't want to die with cleaner sputum. Should physicians withhold prescribing bedaquiline until greater scientific certainty is achieved? How do patients and individual physicians make sound risk-benefit determinations

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about this drug in the absence of conventional scientific data? How should physicians weigh the fact that these new drugs will be phenomenally expensive and many patients' insurance companies may require substantial cost-sharing on the part of patients?

The prospect of approving more drugs based on innovative trial designs that diverge from traditional randomized trials puts greater pressure on the post-approval drug and device surveillance systems and the conduct of confirmatory clinical trials. Studies show that manufacturers' commitments to continue studying drugs after approval may be delayed or incomplete. In addition, once a drug is FDA approved for a certain indication, convincing patients to subject themselves to further randomized trials of a drug for that indication can be challenging, because patients can receive the drug directly outside the trial. This will frustrate the medical community's ability to gather the very confirmatory evidence that may be desired. It is perhaps no wonder that the FDA gave the makers of bedaquiline until 2022 to complete confirmatory clinical trial data on the drug's effectiveness in tuberculosis. Systematic screening for safety issues through the Sentinel initiative or medical device registries shows promise, but these efforts are still relatively novel and researchers like the ones in my Division at Brigham and Women's Hospital are still working out the proper methods to make sure the safety surveillance can be accomplished in a reliable manner.

In summary, the prospect that researchers may be able to design new ways of conducting clinical trials of investigational drugs is exciting, and I hope that the best of these truncated designs are indeed proven to work and provide the same level of confidence as standard randomized trials. Increasing the efficiency of drug development is an important goal. However, the FDA already has the flexibility in its laws and regulations to integrate validated

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innovative study designs and validated biomarkers into its review process. Indeed, the FDA already exercises this flexibility to remarkable extent, providing numerous pathways for important new drugs treating unmet medical needs to be approved in a timely manner on the basis of single-arm, uncontrolled, unblinded trials when necessary. If regulators and others in the medical community are still skeptical about certain biomarkers and clinical trial designs, it's probably because the science supporting them is still in its infancy, in which case forcing approval of the drugs or devices to which they are applied would be dangerous for patients and problematic for physicians.

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Mr. PITTS. Chair thanks the gentleman.

Chair now recognizes Mr. Murray, 5 minutes for an opening statement.

STATEMENT OF BILL MURRAY

Mr. MURRAY. Chairman Pitts, Ranking Member Pallone, and subcommittee members, thank you for the opportunity to testify. My name is Bill Murray, and I am president and CEO of the Medical Device Innovation Consortium. During my 25 years in this industry, I have had the opportunity to lead multibillion-dollar global businesses as well as two early stage companies. These innovative businesses were founded on technology developed in the United States. In recent years, however, these businesses have faced a more difficult regulatory and reimbursement environment in the United States which is challenging our country's position as a global leader in medical device innovation.

I applaud the committee's bipartisan leadership in initiating the 21st Century Cures Call to Action and its commitment for finding solutions to help the U.S. healthcare industry maintain global leadership.

MDIC is a public-private partnership between Government agencies including FDA, CMS, and NIH, non-profits, and industry. MDIC is focused on the medical device ecosystem. We collaborate on advancing regulatory science, by which I mean the tools, standards, and approaches that regulators and innovators use in the development and review of medical devices. We believe that improving regulatory science will offer concrete ways to make patient access to new medical technologies faster, safer, and more cost effective.

Clinical trials are amongst the biggest challenges. The time, complexity, and cost of conducting clinical trials, along with the uncertainty of outcomes, makes them a challenge for both regulators and innovators. And based on a survey of over 200 medical device technology companies, it takes an average of 6 ½ years and $36 million before a new class 3 device even reaches the pivotal study.

We need new approaches if we are to continue fostering innovation. MDIC's goal is to improve the safety and effectiveness of products being introduced to the market, reduce clinical trial timelines and costs, and give U.S. patients earlier access to beneficial technologies.

MDIC's work includes several high priority initiatives. First, MDIC is working to improve the design of clinical trials. Medical device clinical trials are increasingly complicated. MDIC is examining current trial designs to better understand how much of the collected data are used and the ways in which clinical trials may be unnecessarily complex. We are exploring possible alternative trial designs that still supply high quality data on the safety and effectiveness of medical devices.

MDIC is also supportive of FDA Center for Devices and Radiological Health, efforts to balance pre- and postmarket data requirements. Providing the reasonable threshold for clinical data during the pre-market process while continuing to collect data in the postmarket setting is a win for patients and innovators.

Second, MDIC is investigating ways to reduce the barriers to conducting early feasibility studies in the United States. These first in human studies are a critical step in the approval process of many new medical devices. But increasingly, they are performed outside the United States. The reasons for this include economic incentives offered by other countries for companies to invest abroad, but they also include concerns the regulatory approval process is slower, less predictable, and less flexible than the United States. As a result, U.S. patients often have to wait longer for access to new medical devices.

CDRH recognizes this issue and has taken initial steps to address it through a new policy in 2012. MDIC is building on that work by exploring new methods and tools that support early feasibility studies, such as incorporating validated computational modeling and simulation data into the assessment process. We feel strongly that American patients should be the first to benefit from cutting-edge American technologies.

Third, MDIC is conducting research to better understand the data on patient preferences about the benefits and risks of medical devices. Supported by funding from FDA, MDIC is developing a catalog of scientifically valid ways to measure patient perspectives, and we are developing a framework that can support the use of the data in the regulatory process.

Fourth, MDIC is convening experts to help the medical device industry harness the power of computational modeling and simulation. Currently, medical devices lag behind such fields as aerospace and automotive in the use of modeling and simulation tools. The development and use of regulatory-grade tools has the potential to revolutionize the field, enabling developers to generate more ground-breaking ideas, test them with greater confidence, and bring them to patients more safely and quickly, while reducing the costs of clinical trials. Moreover, modeling and simulation may soon play a larger role in the treatment planning and the realization of personalized medicine in the clinic.

MDIC is making progress on these important initiatives, but more needs to be done. We encourage Congress to support efforts to strengthen regulatory science and facilitate public-private partnership collaborations to improve the innovation environment in the United States.

Thank you again for the opportunity to testify about MDIC's collaborative efforts to support medical device innovation that will benefit patients. I will be happy to answer any questions.

[The prepared statement of Mr. Murray follows:]

Testimony of Bill Murray
President & CEO, Medical Device Innovation Consortium

House Committee on Energy and Commerce
Subcommittee on Health
Hearing on:
"21st Century Cures: Modernizing Clinical Trials"
Wednesday, July 9, 2014

Introduction

Chairman Pitts, Ranking Member Pallone, and Subcommittee Members: Thank you for the opportunity to testify before you this morning. My name is Bill Murray, and I am President & CEO of the Medical Device Innovation Consortium. During my 25 years in this industry, I have had the opportunity to lead multibillion-dollar global businesses at Medtronic and Applied Biosystems, as well as two venture capital-backed early-stage companies, ReShape Medical and Envoy Medical. I have also served on the boards of several other companies. While I have been fortunate to learn from a great diversity of experiences through these leadership opportunities, one core aspect has been consistent: All of these innovative businesses were founded on technology developed in the United States. In recent years, however, all of these businesses have faced a more difficult regulatory and reimbursement environment in the U.S., which is challenging our country's position as a global leader in medical device innovation. I applaud the Committee's bipartisan leadership in initiating the 21st Century Cures Call to Action, and its commitment to finding solutions that will ensure that the U.S. healthcare industry is best equipped to maintain global leadership and empowered to deliver the next generation of medical products that will help U.S. patients and the overall healthcare system.

Background on the Medical Device Innovation Consortium

MDIC is a public-private partnership between government agencies, including the NIH, CMS, and FDA; patient advocacy and other nonprofit groups; and industry. MDIC is the only such partnership focused exclusively on the medical device ecosystem. Our mission is to collaborate on advancing "regulatory science," by which I mean the tools, standards, and approaches that regulators and innovators use in the development, assessment, and review of medical devices. MDIC represents a new, collaborative approach to improving the methods used to regulate new medical device innovations. We believe that our focus on improving regulatory science will offer concrete ways to make patient access to new technologies faster, safer, and more cost-effective.

Medical devices play a unique role in healthcare. While medical devices are a small percentage of healthcare spending, they touch many different aspects of patient care. They range from surgical instruments and implantable devices to high-tech molecular diagnostic systems and imaging equipment. Today, the category of medical devices also includes emerging digital technologies and sensors that enable telemedicine and remote healthcare. The pace of new innovations far exceeds all historical precedent. Medical devices not only restore health and extend life by treating many of the most challenging chronic and life-threatening diseases; they also enable new cost-effective ways to deliver healthcare to patients, creating opportunities for improved care at lower cost.

MDIC was formed in late 2012 out of a shared desire on the part of manufacturers and the FDA to address ecosystem-wide challenges facing the U.S. medical device community. Through the vision and leadership of industry leaders and Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, we have been successful in fostering this breakthrough model of cooperation. MDIC is designed to create a collaborative environment where industry, government, and nonprofits can share expertise and resources to advance pre-competitive medical device research, benefiting patients by speeding the rate at which important technologies reach the market.

MDIC's Work to Modernize Clinical Trials and Promote Medical Device Innovation

One of the biggest challenges in the medical device ecosystem are clinical trials. The time, complexity, and cost of conducting clinical trials, along with the uncertainty regarding outcomes, makes clinical trial design and execution a challenge for both regulators and innovators. In the past decade, the demand for high-quality clinical data and the standards by which such data are judged have risen: Our community is expected to conduct more rigorous, evidence-based clinical trials, operate with greater transparency, and do more to inform and share decision-making with patients. In many ways, these changes are benefiting both patients and the industry. However, they have also strained our traditional product development and regulatory assessment systems, which are not sustainable in light of the costs and the uncertainty of outcomes. We need new approaches to clinical development if we are to continue fostering a vibrant innovation ecosystem that is efficient, cost-effective, and economically sustainable. MDIC applauds the committee's focus on finding ways to modernize clinical trials. We

must find ways to improve the clinical development process to ensure that the United States retains our global leadership position in medical innovation.

The good news is that, through MDIC, our stakeholders are proactively collaborating on clinical trial innovation and reform. We believe that clinical trial innovation has the potential to improve the safety and effectiveness of products being introduced into the market, reduce clinical trial timelines and costs, and give U.S. patients earlier access to beneficial innovative technologies. MDIC's work currently includes several high-priority initiatives:

First, MDIC is working to improve the design of clinical trials. Medical device clinical trials are increasingly—and often unnecessarily—complicated. The reasons for this are both varied and poorly understood. They may include inefficiencies in infrastructure, such as missed opportunities for multiple studies to share platforms and resources, the frequently long review cycles and inconsistent requirements of local Institutional Review Boards, and poor subject recruitment by some clinical study sites. Many researchers and regulators also believe that we could be handling data more effectively—that we could save time and money by being more thoughtful about how much and what kind of data is collected in clinical trials, how it is organized and stored, and when it is shared across studies and with the FDA. For example, common data standards and the ability to share information between different electronic health record systems might facilitate fruitful sharing of clinical study data. MDIC is examining current trial designs to better understand which aspects of clinical trials may be needlessly complex, and we are exploring possible alternative trial designs that still supply high-quality data on the safety and effectiveness of medical devices. Our work will include a

survey of our member companies on the amount and type of data that they gather in clinical trials, how much of that data is used, and how much it costs to collect. Our near-term goal is to publish a series of case studies where alternative trial designs were used and how they worked, and to create a menu of alternative trial designs that will explain different design types and when they may be appropriate. Future work will include additional research, such as a survey of physician societies and clinical researchers about trial designs.

Second, MDIC is investigating ways to reduce the barriers to conducting early feasibility studies in the United States. Early feasibility studies, which are also called first-in-human studies, mark the first point at which a new treatment is tested on human subjects. These studies are a critical step in the approval process of many new medical devices, but increasingly, they are performed outside the United States. The reasons for this include powerful economic incentives offered by countries other than the United States for companies to invest abroad, but also a pervasive perception that the regulatory approval process is slower and less predictable in the United States than it is in many other countries. As a result, U.S. patients often have to wait longer than patients elsewhere for access to new medical devices. MDIC feels strongly that American patients should be the first to benefit from cutting-edge American technologies.

The FDA recognizes this need and, in response, issued a new policy in 2012 to make it easier for innovators to start early feasibility studies in the U.S., to do so earlier in device development, and to make certain changes to devices and re-study them without having to receive FDA approval. The FDA has also created a medical device clinical trials program with an acting director in the Center for Devices and Radiological Health

to facilitate these and other innovations. The goal is to reduce the time and cost of the clinical trial enterprise, including the early feasibility phase, while assuring adequate patient protections. Some companies are already taking advantage of the new early feasibility clinical trial policy.

To help address the issue of early feasibility studies, MDIC is conducting an industry survey to help identify the specific barriers that discourage companies from performing these studies in the U.S. We are also exploring new methods and tools to support early feasibility studies, such as templates and best-practice guidelines that could help both innovators and regulators by clarifying how the process should work.

Third, MDIC is conducting research to better understand patient preferences, with the goal of integrating these preferences into the development and regulatory approval of medical devices. Our entire healthcare system is shifting to a model that embraces shared decision-making by informed patients, whose views are valued and considered at every stage of treatment. It makes sense for innovators and regulators to consider patient perspectives as they develop and assess medical devices. After all, one of the most important questions we ask is whether the clinical benefit of a device outweighs its risk. Patients and their families have a deep and personal understanding of what it is like to live with a disease, and they often have valuable insights on how a device could affect their quality of life. In the end, it is patients who must take the risks of medical interventions to obtain the benefits, so their perspectives on benefit-risk tradeoffs should be central to the benefit-risk assessments that are the basis of regulatory approval.

The FDA has acknowledged the potential value of patient preference information in regulatory benefit-risk determinations. In 2012, the agency's Center for Devices and Radiological Health issued guidance[1] for manufacturers on how it makes benefit-risk determinations during the pre-market review of certain medical devices. Significantly, FDA emphasized that "patient tolerance for risk and perspective on benefit" is an important consideration. However, this important guidance document does not discuss how such information on patient tolerance of risks and valuing of benefits can be collected or presented to the FDA.

One of MDIC's first major efforts will be on how to measure information on patient preferences and incorporate that data into the regulatory assessment of new medical devices. This work is being funded by the FDA and builds upon the findings of a public workshop hosted by the agency last fall. MDIC's Patient-Centered Benefit-Risk (PCBR) Project will have three major deliverables: First, we will develop a catalog of scientifically valid ways to reliably assess patient views on the potential risks and benefits of specific devices. Second, we will develop a framework for thinking about how to incorporate patient preferences into regulatory benefit-risk assessments. Third, we will produce an analysis of gaps in our current ability to collect and use patient preference data, with a research agenda to address those gaps. The PCBR Project team working on these deliverables includes knowledgeable participants from CDRH, industry, patient advocacy groups, and academia. MDIC plans to share our work on patient preferences

[1] "Guidance for Industry and Food and Drug Administration Staff - Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications." FDA. March 28, 2012. http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm267829.htm.

publicly in early 2015, with the goal that CDRH might choose to build off this work in future guidance documents and in regulatory decision-making. We also anticipate that others, including innovators, payers, patient care organizations, advocacy groups, and academics, will find our catalog of methods for obtaining patient preference information, our thinking about how to use patient preference information in benefit-risk assessment, and the agenda that comes out of our gap analysis helpful in their efforts to improve patient outcomes and make healthcare more patient-centered.

Fourth, MDIC is convening experts to help the medical device industry harness the power of computational modeling and simulation. Modeling and simulation have the potential to revolutionize the field, enabling medical device developers to generate more groundbreaking ideas, test them with greater confidence and at lower cost, and bring them to patients more safely and quickly. Moreover, with accelerated use in development and evaluation, it is conceivable that modeling and simulation will play a larger role in treatment planning and fully realizing personalized medicine in the clinic. Currently, though, the medical device industry lags behind such fields as aerospace and automotive engineering in the use of these tools.

MDIC members share a vision of using modeling and simulation to accelerate medical device innovation. We are working to achieve the consistent application of validated computational modeling and simulation in device development and regulation. We aim to use these tools to evaluate new and emerging technologies, and to develop state-of-the-art preclinical methods for assessing device safety and performance. We are studying how the incorporation of virtual patients might inform clinical trial design, making clinical trials more efficient and potentially reducing their size. To achieve these

goals, we are working to define, standardize, and educate the medical device community on validation requirements for the use of modeling and simulation in device development and regulatory submission.

Recommendations to Support Medical Device Innovation

While we are very pleased with the progress MDIC is making on these important initiatives, much more needs to be done. Regulatory science is a nascent field that will benefit from a sustained strategic investment throughout the design, development, regulatory, and reimbursement product lifecycle to ensure that U. S. citizens have timely access to high-quality, safe, and effective American innovations. We encourage Congress to support these efforts to strengthen regulatory science to help improve the environment for medical innovation here in the United States.

There are three key steps Congress could take to support this work and work by other innovative partnerships. First, create grants for public-private partnerships that effectively harness the brainpower of both the public and private sectors to address a public health need. Second, remove barriers to public health agency participation in these types of partnerships. Currently, the Federal Advisory Committee and Paperwork Reduction Acts, together with technology transfer statutes, increase the time and complexity involved in establishing and managing organizations like MDIC. Finally, allow federal, industry, and nonprofit researchers to collaborate freely on work that is supported in part by industry. Hesitation to use federal gift authority means that it is often difficult for our best minds to work together unless the partnership was specifically

established by Congress, as in the Foundation for the NIH, or funded by a federal agency. Without requiring Congressional action, stakeholders and government experts should be liberated to identify a need, come together to address it, and then dissolve the partnership once the public health need has been addressed. Public-private partnerships can be nimble, efficient, and responsive, but only if government, nonprofit, and industry participants are allowed to participate freely, work together closely, and invest wisely. These partnerships are unique and address a unique need. There are no easy questions left in medicine. We need big collaborations to conduct big science, and to rapidly and efficiently improve human health. Partnerships allow each sector—patients, foundations, industry, and the government—to vote with their feet, spending their time, ideas, and resources only on those partnerships that accurately identify the outstanding problems and creatively search for the solutions.

Thank you again for the opportunity to testify and educate the Committee and stakeholders about MDIC's collaborative efforts to advance pre-competitive medical research that will benefit patients.

I will be happy to answer any questions.

Summary of Testimony on 21st Century Cures: Modernizing Clinical Trials
Bill Murray
President & CEO, Medical Device Innovation Consortium (MDIC)
Wednesday, July 9, 2014

MDIC is an unprecedented public-private partnership between government agencies, patient advocacy and other nonprofit groups, and industry. MDIC is the only such partnership focused exclusively on the medical device ecosystem. Our mission is to collaborate on advancing regulatory science. We believe that we can offer concrete ways to make patient access to new technologies faster, safer, and more cost-effective.

In recent years, medical device businesses have faced a more difficult regulatory and reimbursement environment in the United States, which is challenging our country's position as a global leader in medical device innovation. I applaud the Committee's bipartisan leadership in initiating the 21st Century Cures Call to Action.

Clinical trials are among the biggest challenges in the medical device ecosystem. The time, complexity, and cost of conducting clinical trials, along with the uncertainty regarding outcomes, makes clinical trial design and execution a challenge for both regulators and innovators. We need new approaches to clinical development if we are to continue fostering a vibrant innovation ecosystem that is efficient, cost-effective, and economically sustainable.

MDIC's stakeholders are proactively collaborating on clinical trial innovation and reform. We believe that clinical trial innovation has the potential to improve the safety and effectiveness of products being introduced into the market, reduce clinical trial timelines and costs, and give U.S. patients earlier access to beneficial innovative technologies.

Our high-priority initiatives include:

- Improving the design of clinical trials.
- Reducing the barriers to conducting early feasibility studies in the United States.
- Conducting research to better understand patient preferences, with the goal of integrating these preferences into the development and regulatory approval of medical devices.
- Convening experts to help the medical device industry harness the power of computational modeling and simulation in clinical trials.

To support medical device innovation in the United States, we recommend that Congress:

- Support efforts to strengthen regulatory science.
- Create grants for public-private partnerships that effectively harness the brainpower of both the public and private sectors to address a public health need.
- Remove barriers to public health agency participation in these types of partnerships.
- Allow federal, industry, and nonprofit researchers to collaborate freely on work that is supported in part by industry.

Mr. PITTS. Chair thanks the gentleman.

And now recognize Dr. Siegel, 5 minutes for an opening statement.

STATEMENT OF JAY P. SIEGEL

Mr. SIEGEL. Thank you, Chairman Pitts and Ranking Member Pallone and members of the committee.

I have been working on clinic trial improvements for over 30 years from the diverse perspective of a senior U.S.——

Mr. PITTS. Is your mic on? Thank you.

Mr. SIEGEL. I have been working on clinical trial improvements for over 30 years, from the diverse perspectives of a senior USFDA official, an industry R&D leader at Johnson & Johnson, and a participant in many broad collaborations, including the International Collaboration for Harmonization, the Society for Clinical Trials, and the Clinical Trials Transformation Initiative.

I applaud and thank the committee for the 21st Century Cures Initiative and today's focus on clinical trials modernization.

Our clinical research enterprise is critically important for medical progress, but was largely designed for conditions that prevailed years or decades ago. We have before us new tools and opportunities to modernize it and thereby to usher in a new era of efficient translation of scientific advances and to medical advances in 21st century cures.

I will briefly discuss four of these opportunities: Use of electronic health records, use of biomarkers, creation and use of clinical trial networks and consortia, and engaging patients as collaborators in the research process.

The adoption of electronic health records provides the potential to collect data efficiently in the settings in which health care is being delivered, creating a learning healthcare system. Large scale registries of patients with a shared condition can be constructed, allowing studies of disease course, risk factors, biomarkers, and treatment effects. The powerful tool of randomization could be applied to such cohorts, creating large simple clinical trials in the care setting. The resultant enhancement of the ability to learn about the effects of medicinal products while in clinical use could allow earlier availability of important new therapies with assurance that additional information would be collected reliably and efficiently after approval.

Full realization of the promise that electronic health record enhanced research holds will require addressing several needs, including standardization, interoperability, and data quality of the systems; research into how best to compile and use the data; and reassessment of the regulatory frameworks that protect patients.

The rapidly increasing ability to collect and analyze genomic, proteomic imaging and other information allow incorporating that information into clinical trials as biomarkers. One valuable use of biomarkers in clinical trials is as surrogate end points, which, if reasonably likely to predict clinical benefit, can support the accelerated approval of new therapies. The success of accelerated approvals in bringing important new drugs to patients in need sooner, together with the ability to measure many new biomarkers, suggests that wider usage of biomarkers for accelerated approval would be

beneficial. In the FDA Safety and Innovation Act of 2012, Congress encouraged such wider usage.

Use of biomarkers for patient subgrouping and response monitoring can crucially enhance several other aspects of clinical research, including personalized medicine research, disease prevention research, and adaptive clinical trials. Government, in partnership with academia, patient groups, and industry, can create and operate clinical trial networks that provide a rapid and efficient means for assessing promising new therapies.

Networks have already led to substantial advances in clinical research, and there is potential to address more disease, to create broad consortia, and to utilize powerful new tools, such as electronic health record-based trials and ongoing biomarker-driven adaptive design trials, such as Lung-MAP.

Patients bring to clinical research valuable perspectives and insights and often strong motivation to contribute. Enhanced participation of patients in the design and conduct of clinical trials can be expected to improve many aspects of trials. Patient-reported outcomes together with patient-informed risk/benefit assessments should play a larger role in clinical trials and product development.

Additionally, efforts to involve more patients in clinical research will help unleash the power of a learning healthcare system while helping ensure that our medical knowledge is derived from the experience of a more diverse and representative population.

Mr. Chairman, I thank you and the committee for your invitation and your attention.

[The prepared statement of Mr. Siegel follows:]

STATEMENT OF JAY P. SIEGEL, M.D.

JOHNSON & JOHNSON

BEFORE THE HOUSE COMMITTEE

ON

ENERGY AND COMMERCE

CLINICAL TRIAL MODERNIZATION

JULY 9, 2014

Testimony of Jay P. Siegel, M.D.

Speaking on behalf of Johnson & Johnson

July 9, 2014

Good morning, Mr. Chairman and Members of the Committee. My name is Dr. Jay Siegel, and I am pleased to come before you today to offer a perspective on clinical trial modernization. As a physician, scientist, clinical trialist, research and development leader, and former public health officer, I am deeply troubled by two paradoxes. First, despite rapidly expanding biological knowledge and technology and increasing private spending on drug development, fewer new drugs reach patients each year than decades ago. Second, despite massive amounts of valuable medical data being generated and recorded every day, only a tiny fraction is being used to advance the health and welfare of patients by enhancing medical knowledge. I applaud this committee for its efforts in the 21st Century Cures Initiative and specifically for this hearing on clinical trial modernization as I believe that we now face an extraordinary opportunity to reinvent our approach to clinical trials and, as a result, to greatly increase the quality of medical care and the quality of life itself.

By way of introduction, I studied biology at the California Institute of Technology and received my medical degree from Stanford University with post-doctoral training at Stanford and the University of California, San Francisco. I worked 20 years regulating biologics at the Food and Drug Administration (FDA), including as the founding Director of the Division of Clinical Trial Design and Analysis. While at FDA, I had the privilege of working with leading clinical researchers in all areas of medicine, helping design and assess studies, and of helping create dozens of national and international guidance documents relevant to clinical trials.

For the past 11 years, I have served in various R&D leadership roles at Johnson and Johnson, where I am currently Chief Biotechnology Officer, and Head of Scientific Strategy and Policy. I have remained deeply engaged in clinical research issues and oversight, both internally and through participation in various organizations, including

the Biotechnology Industry Organization, the Society for Clinical Trials, and the Clinical Trials Transformation Initiative.

Clinical trials can be an essential tool in addressing the aforementioned paradoxes by turning scientific advances into medical advances and by ensuring that, as medical care is delivered, we learn from the collective experience. The way we currently think about, design, conduct, analyze, and regulate clinical trials has roots in an earlier era, when we lacked some powerful tools now available. We now have the opportunity to greatly enhance the power, efficiency and effectiveness of clinical trials. I will focus on four factors that enable such advances:

1. Use of electronic health records (eHR)
2. Use of biomarkers (e.g., genomics and proteomics), imaging, and informatics
3. Clinical trial networks, consortia, and disease-specific registries
4. Engaging patients as collaborators in the research process

1. ELECTRONIC HEALTH RECORDS AND RESEARCH IN THE CLINICAL CARE SETTING

The broad adoption of eHR enhances the potential to study health care efficiently in the settings in which it is being delivered. With use of eHR clinical research can be embedded into clinical care, creating what has been termed the learning medical system.

Electronic health records, if appropriately standardized and quality controlled, could provide highly valuable information to improve medical care. Efficient data collection through eHR could be augmented, where needed, with study-specific data collection forms integrated into the health record computer in the physician's office.

Using eHR, large scale registries of patients with a shared chronic condition could be constructed and data could be used for various purposes including studying risk factors and progression of the condition, to assess safety and other outcomes of treatment

alternatives in use, to validate biomarkers, and to identify potential participants for specific trials. The collection of data by eHR could be supplemented, when needed, with the power of random assignment to treatment alternatives to enable large simple randomized clinical trials conducted in care delivery settings, increasing the likelihood their results and learnings can be generalized to medical practice.

Perhaps the most valuable use of eHR-based studies in the clinical care setting will be to study interventions that are already in use (FDA approved, as needed), but where the best choice among available interventions is uncertain. However, eHR-based trials, particularly when employing supplemental data collection and randomization also have substantial potential to facilitate development of new medicinal products.

The availability of large registries would facilitate expansion of one of the more promising new approaches to clinical research – ongoing, adaptive clinical trials into which new, experimental therapies can be inserted for study. Based both on biomarker data and accumulating results, such adaptive trials can preferentially allocate subjects to promising treatments and discard non-beneficial treatments at an early timepoint. The recently launched Lung-MAP trial to evaluate therapies for squamous cell lung cancer is an example of such a trial. Similar approaches, facilitated by eHR (as well as by biomarkers and consortia), could greatly enhance the medical progress and development of treatments and cures across a broad range of diseases.

The power of eHR-based studies to enhance the ability to learn about the effects of medicinal products *after* market authorization (i.e., FDA approval) can have a profoundly positive effect on the frequency, speed, and efficiency of bringing new products, and new cures, to the marketplace. Information about a medical product's effects increases throughout its clinical usage, pre- and post-market. A key to effective regulation is the determination of where along that timeline sufficient information exists to warrant marketing authorization. The risks of approving products too early include the possibility that information important to the safe and effective use will be learned too late or not at all. But these risks must be balanced against the downsides of delaying access of patients

to important new medications by requiring additional information before approval. Also, the increased premarket costs and timelines that result from delaying approval to obtain more information can decrease the incentives for private investment in developing 21st Century Cures.

Given current limitations on the ability to gather information after marketing, data requirements (safety and otherwise) premarketing have been understandably and appropriately extensive. As eHR and learning health care systems enhance our ability to capture accurate information about a product's effect while on market, the risk of earlier approvals will diminish. Provided the regulatory process responds to this decreased risk, the result will be earlier availability of important therapies and increased investment in new treatments.

Realization of the potential for eHR-enhanced research in the clinical practice setting to augment the goals of the 21st Century Cures Initiative can be accelerated and optimized by addressing some key needs, including:

- *Standardization and interoperability of the eHR systems* so patients can be tracked and data compiled across multiple systems (e.g., different primary care systems, hospital records, cancer registries). Such standardization has been implemented in some countries (Scotland, Nordic countries) but is not in practice in the US.
- *Enhanced quality of data capture in eHR.* Training, standards, and incentives for physicians to capture complete and accurate data could enhance both medical care and medical research.
- *Research into how best to compile eHR data and use it both in clinical trials and in observational studies.* The Observational Medical Outcomes Partnership (OMOP), a public-private partnership including industry, FDA, and academics, has done much work in this area. More work remains and this should be a research priority.
- *Educating and incentivizing clinicians to become part of the learning system,* embedding studies into their process of clinical care.

- *Reassessing legal and regulatory frameworks to protect patients.* Current systems were designed in an earlier era and are likely not optimized to protect patients, or to ensure that they also support advances of clinical research utilizing eHR.

2. BIOMARKERS, IMAGING, AND INFORMATICS

Tremendous advances in our ability to collect and analyze many types of information about a patient and a disease state have greatly outpaced our ability to utilize such information. In particular, advances in genomics, proteomics and imaging hold the prospect to improve many aspects of how clinical trials are used in the development of new treatments.

I will briefly discuss four areas that could benefit from increased utilization in clinical trials of biomarkers and imaging:

- Accelerated approvals
- Personalized medicine
- Disease prevention and interception
- Adaptive design trials

Accelerated approval (biomarkers as surrogate endpoints)

The most reliable measures of efficacy of a treatment are direct measures of substantial patient benefit such as prolonged survival. But trials to assess such outcomes may need to be large and lengthy and their findings may be confounded by other therapies a patient may receive over the course of his or her disease. Use of biomarkers and imaging results that predict clinical benefit as surrogate measures of efficacy may allow more efficient clinical trials to support product approval.

Recognizing the potential utility of such surrogates, FDA, with congressional support, has for over two decades permitted use not only of surrogate endpoints validated to predict benefit, but also of those found to be reasonably likely to predict clinical benefit in serious diseases. Effects on the latter type of endpoint can support accelerated approval with a post-approval commitment to confirm benefit.

The acceptability of a surrogate as being reasonably likely to predict benefit is a matter of regulatory judgment. A key component of that judgment is assessment of the risk of being incorrect; that is, of approving a product based upon a surrogate endpoint when clinical benefit did not ensue. With the advent of new biomarkers and imaging modalities as potential surrogate endpoints, two arguments indicate that there would be net benefit to greater use of accelerated approval based on clinical trials with biomarker or imaging endpoints as surrogate endpoints. First, the vast majority of drugs approved to date under accelerated approval have had their benefit confirmed post-marketing. The benefits of accelerating, often by years, the availability of many important new therapies for serious diseases greatly outweighs the harms in those few cases where benefits have not been confirmed and accelerated approval was withdrawn. The fact that where it has been used, accelerated approval has brought tremendously positive results suggests that society would benefit from broader usage of accelerated approval, even where the risk of being wrong may be somewhat greater. Second, as noted above, the advent of eHR gives us a powerful new tool to assess drug effects in the post-marketing period. This reduces the risk that accelerated approval will lead to a situation in which actual benefits cannot be assessed or cannot be assessed in a timely manner.

Recognizing the desirability of broader use of accelerated approval, Congress, in the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, included language expanding the types of evidence FDA can use to assess whether a surrogate endpoint is likely to predict clinical benefit and encouraged usage of a broader variety of endpoints for accelerated approval, asking FDA to

> *"... implement more broadly, effective processes for the expedited development and review of innovative new medicines intended to address unmet medical needs*

for serious or life-threatening diseases or conditions, including those for rare diseases or conditions, using a broad range of surrogate or clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate."

It is too early to assess the impact of FDASIA on accelerated approvals. Given the potential benefits of broader usage of accelerated approval, it would be of value to follow up on efforts to realize the intent of FDASIA.

Personalized medicine (use of biomarkers to identify the best treatment for each patient)

Advances in next generation sequencing, imaging, and molecular diagnostics (e.g., proteomics), are contributing to our understanding of how and why drugs may have different effects in different individuals with the same diagnosis. Use of such biomarkers and imaging for entry and subset analysis in clinical trials will increase our ability to target treatments to those patients who will benefit most and/or be least likely harmed.

Disease prevention and interception (use of biomarkers to identify individuals at risk)

Advances in understanding the genetic and molecular basis of many diseases present an opportunity for advances in disease prevention and interception (i.e., the diagnosis and treatment of diseases at early stages to prevent progression and serious manifestations). The health benefits of disease prevention and interception over treatment are obvious. Prevention and interception also often offer substantial cost avoidance compared with treatment, although the savings may be delayed.

Despite these substantial opportunities, there have been relatively few clinical trials studying the prevention and interception of chronic diseases and cancer. One reason is that such trials can be rather large and lengthy, as it may be necessary to follow many research participants for a long time in order to see disease develop or progress in sufficiently large numbers to draw conclusions about an intervention. Biomarkers and imaging may help address these operational challenges of prevention trials. Such tests

can be used to identify patients at high risk for developing disease or progressing and may also be useful to detect progression.

Adaptive design trials (se of biomarker data to modify a trial)

The conventional approach to clinical trials is to lock in the design from the beginning. This approach lowers the risk of several types of bias. However, it potentially sacrifices efficiency by failing to make use of learnings during a trial to optimize design of the remainder of the trial.

In recent years, methodological advances have allowed greater modification of trials while in progress with limited risk of bias. Such trial designs are called adaptive designs. Advances in biomarkers and imaging enable adaptive designs by providing real time assessments of response to the intervention that can be used to modify the trial without having to wait for ultimate outcomes such as death.

Adaptive trials offer the opportunity to increase the efficiency of trials in translating science into medical knowledge, to accelerate drug development, and to ensure that more of the participants receive the more promising therapy. More experience with such trials should be encouraged as it will undoubtedly teach lessons on how best to deploy them. The Lung-MAP trial, referenced above, is one innovative example of a biomarker-driven, adaptive trial.

Implementation of biomarker usage other than for accelerated approval

Given that personalized medicine, disease prevention and interception, and adaptive trial designs have high potential value, the development and study of biomarkers and imaging to support these ends should be encouraged. Where such usages are shown to be associated with improved clinical outcomes, the regulatory process should be (and generally is) sufficiently flexible to allow that information to be incorporated into medical knowledge and practice.

3. CLINICAL TRIAL NETWORKS, CONSORTIA, AND DISEASE-SPECIFIC REGISTRIES

Government, in partnership with academia, patient groups, and industry can create and operate clinical trial networks that provide a rapid and efficient means for assessing new therapies either through ongoing large adaptive trials or through a series of trials. Well-run clinical trial networks can reduce the operational barriers, costs, and times of starting and conducting trials. The federal government can and should play an important role in creating and governing such networks, and involvement of a broader public-private partnership can help ensure that needs are met by bringing together experts and interested parties from diverse perspectives.

In some disease settings it may be appropriate for such a consortium to conduct a single ongoing adaptive trial to study many therapies (such as Lung MAP); in other settings it may be more practical to conduct a series of trials. Such consortia could and should also play a key role in creation and use of eHR-based registries and trials as discussed above.

Clinical trial networks have been operational and have achieved success in several disease areas. Currently, the creation of a broad collaboration or consortium to develop a registry, to identify cohorts, and to design and conduct trials is being implemented through IMI-EPOC-AD: the Innovative Medicines Initiative European platform for Proof of Concept for prevention in Alzheimer's disease.

4. ENGAGEMENT OF PATIENTS AS COLLABORATORS IN THE RESEARCH PROCESS

The traditional paradigm for clinical research places patients in the position of subjects – a relatively passive role. But patients bring to the clinical research far more than a disease or condition; they bring valuable perspectives and insights. Furthermore, many

patients are strongly motivated to participate in research, both to benefit their own care and altruistically, to benefit future patients with a similar condition. Enhanced patient engagement can benefit the clinical trial process in various ways, including the following:

- *Patient-reported outcomes:* Often investigators and regulators have defaulted to use of outcome measures that can be objectively measured. However, the outcomes most important to patients, those reflecting how they feel, are generally best obtained directly from patients.
- *Patient-informed risk-benefit assessments:* Usage of virtually all therapies is associated with some risk of adverse effects. So in the regulatory decision process, safety is not an absolute; rather the acceptability of the safety profile of an intervention must be determined in the context of potential benefits. Patients can provide a unique and extremely valuable perspective on the impact and relative value of various demonstrated benefits and risks.
- *Improved trial design*: Patient involvement in trial design can enhance recruitment, adherence, relevance, and tolerability of trials.
- *Enhanced enrolment of patients in clinical research*: A critical prerequisite to developing an effective learning medical system with medical research embedded into care settings is to expand and diversify enrolment into clinical trials. We must move from a situation in which study volunteers are a select, rather non-representative group of patients to one in which they are a much larger, diverse, broadly representative group who represent well those to whom results will be generalized. That end can best be accomplished if all involved parties, including government agencies such as NIH, NSF, and FDA work to engage the public, educating people about the value of participation in clinical research while dispelling common misperceptions. Broader voluntary participation in trials will improve both their speed and their generalizability, bringing treatments to patients sooner, and with more information.

CONCLUDING REMARKS

Again, I wish to thank the Committee for its attention to this important matter. As I have described, several opportunities are before us, through advances in clinical trials, to improve the translation of scientific advances into medical advances and patient cures, and to ensure that more of the vast amount of medical data created and recorded every day are used to improve the care of patients and advance medical knowledge. The result will be nothing less than longer and healthier lives.

Executive Summary of Testimony of Jay P. Siegel, M.D.
Speaking on Behalf of Johnson & Johnson
House Committee on Energy and Commerce, July 9, 2014

Clinical trials are the tools by which our society translates scientific advances and product discoveries into advances in medical care. Johnson & Johnson welcomes the opportunity to participate in efforts intended to improve the effectiveness and efficiency of clinical trials. There are various opportunities for such improvements that will greatly facilitate advances in health care. We emphasize four areas of opportunity.

First, the adoption of electronic health records (eHR) can enable great advances in research in the clinical care setting. Properly deployed, eHR can enable extensive and rapid data collection with limited disruption to the clinical care process. Large patient registries can be created to study a specific disease and its treatments and to enable randomized trials employing eHR in data collection. Improvement in ability to obtain data from use of products post-approval should, in some cases, enable earlier approval and availability of valuable new therapies. Realizing this potential will require addressing several issues, including: standardization and data quality of eHR systems, enhanced provider and patient education and participation, research into how best to compile and use eHR data, and reassessment of regulatory frameworks.

Second, scientific advances in identifying biomarkers and imaging modalities, when applied in clinical trials, can greatly enhance our learning and progress. Increased usage of biomarkers for accelerated approval can be expected to accelerate availability of important new therapies more broadly, as it has for HIV infection and cancer. Increased usage of biomarkers in clinical trials can also be expected to advance: 1) personalized medicine, by identifying patient characteristics that help determine the best therapy, 2) the study of disease prevention or early treatment (interception) by identifying patients at substantial risk of developing disease or experiencing progression, and 3) the utility of adaptive trial designs, in which information learned during a trial is used to improve the trial design and ability to address key questions.

Third, creation of clinical trial networks involving consortia of government, academia, patient groups and industry can provide a rapid and efficient means for assessing new therapies, in either ongoing large adaptive trials or through a series of trials. Such consortia could also assemble and utilize eHR-based registries.

Fourth, increased engagement of patients as collaborators in the research process can bring about improvements in how we measure the effects of an intervention (patient reported outcomes), in how we assess risks vs. benefits, and in clinical trial recruitment, adherence, relevance, and acceptability. Broad education about the benefits of clinical trial participation could help bring about greater participation, facilitating creation of a learning health care system and accelerating advances in medical care.

Mr. PITTS. Chair thanks the gentleman.

Now recognize Dr. Herbst, 5 minutes for an opening statement.

STATEMENT OF ROY HERBST

Mr. HERBST. Good morning, Chairman Upton, Ranking Member Waxman, Subcommittee Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. Thank you for inviting me today to share my experience regarding innovative clinical trials for cancer patients. I am Dr. Roy Herbst, and in my role as chief of oncology at Yale, I care for patients with lung cancer, conduct and collaborate on basic research, and work on clinical trials from phase I, first in human, to phase III. Over the last 2 years, I have been working with the Friends of Cancer Research, which was founded and is led by Ellen Siegel, the National Cancer Institute, SWOG, a cancer cooperative group, and the FDA on an innovative public-private partnership approach to clinical trials. And I am honored to be invited to participate in this important hearing today.

Cancer is the second most common cause of death in the United States, with over half a million Americans expected to die of this disease in 2014. Cancer is a disease that is accompanied by much pain and suffering, loss of life and productivity. Despite advancements in surgery and drug therapy, many cancers remain incurable. Lung cancer, the number one cause of cancer death, is one such disease. And, as a specialist in this area, I often see patients with advanced disease who have very limited treatment options. For this reason, together with my colleagues in the field, we strive to develop new therapies for these patients so that we may provide them with a cure or at least with more quality of life and time with their families. I am working hard to personalize care; I want to match a patient's tumor profile with a best treatment, with the overarching goal to find ways to provide more active, less toxic, and more cost-effective therapies.

I am happy to say we are making progress. Due to the country's investment in research, in 2014, we can now sequence every gene in a tumor, including the 25,000 protein-coating genes. This is amazing technology and science. However, it remains limited. Why? Because, one, it is still only available to a minority of patients; two, it is expensive and often not covered by insurance; three, the informatics and data-interpretation challenges are overwhelming; and, most importantly, we still do not know how to translate this information into therapeutic benefit.

Hence, clinical trials are essential for this process and the need to modernize for the molecular age is very important. Often clinical trials are limited by numerous challenges, including the startup time, accrual expense, and the need to identify and define subpopulations of patients that makes trial enrollment difficult.

Developing a potential therapy from the initial discovery stage through clinical testing and regulatory approval is a complicated, expensive, and often inefficient process that can take up to 15 years.

Let me give you an example. In recent years, we tried to study a drug that affects 10 percent of patients with lung cancer. That meant we had to screen 100 patients at Yale to find 10; only six

of those patients were then eligible with good enough status to go on the trial; we treated two. That is totally unacceptable, it is not good for the patients, it is not good for the clinical trial, it is not going to advance our cause.

With this in mind, the Lung Cancer Master Protocol, known as Lung-MAP, is an innovative, groundbreaking clinical trial designed to facilitate efficiencies and advance the development of targeted therapies for squamous cell lung cancer of the lung, one of the worst types of this cancer. The concept of a lung map was developed at the 2012 Friends of Cancer Research Brookings conference on clinical cancer research, and at the same time, by the National Cancer Institute Lung Cancer Steering Committee.

Since the release of that initial concept paper through the intense collaboration of many, Lung-MAP was initiated and opened in a very rapid year and a half. The goal is to develop a biologically driven approach, building on the NCI-funded Cancer Genome Atlas, TCGA, to identify targets.

In Lung-MAP, a master protocol will govern how multiple drugs, each targeting a different biomarker, will be tested as potential treatments for lung cancer. Each arm of the study will test a different drug that has been determined to target a unique genetic alteration. The use of cutting-edge screening technology will help identify which patient is a molecular match to each arm. This will create a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs. We want to get the right drug to the right patient at the right time. This is good for patients because it allows them, with as many as 500 sites to be opened around the U.S., to have access to the drugs and allows us to study effects so eventually they can become approved and be available to even more people around the world.

One of the benefits of the Lung-MAP, enrollment efficiency. Grouping these studies under a single trial reduces the overall screen failure that is great for patients. Operational efficiency, a single master protocol can be amended as needed as drugs enter and exit the study without having to stop and restart; cost efficiency, as a result of shared services, utilization of existing infrastructure and avoiding redundancy, this public-private partnership will operate at cost substantially less than individual trials.

This consistency among trials, predictability on the outcome, full transparency with an oversight committee and a drug selection committee benefit to patients, and seamless movement from phase I to II trial design. In fact, the FDA was very closely involved with the idea for this whole concept.

My time is running short. But I will tell you that I hope this committee can help us and with the issue of biomarkers, how to develop better biomarkers for these trials, how to regulate the diagnostics for these trials. Certainly the public-private partnership that we have developed is one that needs to be enhanced and helped and incentivized.

And, of course, finally resources. We have been working with the NCI. And the budget is flat at best. And certainly we want to bring more of those drugs to patients.

So as I conclude, Lung-MAP is a public-private partnership where each sector has committed to do business differently. To-

gether we believe that Lung-MAP can demonstrate a new model for high quality drug development in less time at less cost for more people, and most importantly, improve the lives of patients with lung cancer. I am happy to report the first patient on the study enrolled at Yale yesterday. The shared goal of accelerating the pace in which new drugs are developing is a driving force behind this partnership. We know that this committee shares that goal, and so we thank you for taking on this important 21st Century Cures Initiative. Thank you.

[The prepared statement of Mr. Herbst follows:]

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

FRIENDS of CANCER RESEARCH

21st Century Cures: Modernizing Clinical Trials

Testimony Before
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

Roy Herbst, MD, PhD
Ensign Professor of Medicine and Chief of Medical Oncology and Associate Director for Translational Research,
Yale Cancer Center

Co-Chair
Lung-MAP

July 9, 2014

21st Century Cures: Modernizing Clinical Trials

Testimony of Roy Herbst MD, PhD, Ensign Professor of Medicine and Chief of Medical Oncology and Associate Director for Translational Research, Yale Cancer Center

Good morning, Chairman Upton, Ranking Member Waxman, Subcommittee Chairman Pitts, Ranking Member Pallone, and Members of the sub-committee. Thank you for inviting me today to share my experience regarding innovative clinical trials for cancer patients. My name is Dr. Roy Herbst and I have been working on this problem for nearly 30 years having trained as both an MD and PhD in cancer medicine. I am currently the Ensign Professor of Medicine and Chief of Medical Oncology at the Yale Cancer Center where I am also the Associate Director for Translational research. In my role at Yale, I care for patients with lung cancer, conduct/collaborate on basic research, and work on clinical trials from phase I (first in human) to phase III. Over the last two years I have been working with the Friends of Cancer Research (founded and led by Ellen Sigal), the National Cancer Institute, SWOG, and FDA on an innovative public-private partnership approach to clinical trials- and am honored to be invited to participate in this important hearing today.

Cancer is the second most common cause of death in the US. According to the American Cancer Society, about 585,720 Americans are expected to die of cancer in 2014. Unfortunately many cancers that have spread or become metastatic are currently incurable. Lung cancer is one such incurable cancer and as a specialist in this area I often see patients with advanced disease and work to develop new therapies and cures. This disease is accompanied by much pain and suffering, loss of life and productivity. Twice in my career I personally have seen and been involved in the development of new agents for the treatment of lung cancer that have truly transformed the landscape. In 1997, we began to study drugs that target the epidermal growth factor receptor and noticed that 10-20% of patients experienced extraordinary benefit. However it was not until 2004 that researchers identified the biomarker and learned how to identify that small group of patients who would benefit from the treatment. Patients are still alive from

these initial studies. Today we have the advent of immunotherapies, that provide extraordinary benefits in melanoma, renal, lung and other tumor types, but we still do not know who benefits most. If we knew how to identify these patients in advance we could find ways to provide more effective, less toxic and more cost effective therapies that are tailored to best suit each patient.

Due to our country's investment in research, in 2014 we can now sequence every gene in a tumor including the 25,000 protein coding genes. This is amazing technology and science, but is limited because 1) it is only available to a minority of patients, 2) it is expensive and often not covered by insurance, 3) the informatics and data interpretation challenges are overwhelming, and most importantly 4) we still do not have the ability to translate the information into therapeutic benefit. The medical community remains limited on our abilities to match the right patient to the right drug at the right time. The challenges are multifold- and include issues such as limited knowledge of the distribution of a particular genetic alteration in the patient population as well as cost of trials. For example, I recently conducted a trial in lung cancer with an agent that targets FGFR (Fibroblast growth factor receptor), with a presumptive abnormality in 10-20% of patients. We screened 100 patients to find only 6 with the abnormality, which was much fewer than expected, and inevitably we were only able to enrolled 2 patients on the trial. This type of trial does not help enough patients and also is not conducive to productive research.

Clinical trials need to be modernized for the molecular age. Often clinical trials are limited by numerous challenges including the start-up time, accrual, expense, and the need to identify defined sub-populations of patients that makes trial enrollment difficult. Developing a potential therapy from the initial discovery stage through clinical testing and regulatory approval is a complicated, expensive, and often inefficient process that can take up to 15 years. Only by finding better ways to match drugs with patients and studying them in large and diverse populations can we help more patients with this disease

and get drugs approved. Modernizing this process with innovative approaches and new clinical trial designs is of high importance.

With this need in mind, the Lung-MAP: is an innovative, groundbreaking clinical trial designed to facilitate efficiencies and advance the development of targeted therapies for squamous cell cancer of the lung. It provides a mechanism to genomically screening large but homogeneous cancer populations and subsequently assigning and accruing patients simultaneously to a multi-sub-study "Master Protocol", resulting in a prospective, randomized phase II/III registration protocol. It addresses unmet medical needs for squamous cell lung cancer (commonly diagnosed in those with a history of smoking) and will provide answers to current questions across all of drug development, including how to develop drugs for uncommon-rare genotypes, how to apply broad-based next generation screening (NGS), and how to achieve acceptable turn-around times for molecular testing for therapy initiation?

There are previous examples of this new approach to clinical trial design focused on testing driven by the presence of biomarkers in the study population. First, patients are screened for the presence of biomarkers and then are assigned to sub-studies with investigational drugs targeting the biomarkers. These targeted therapies hold promise for improved efficacy, but for traditional single component studies many patients may need to be screened before enough patients harboring the necessary genomic alteration are available for the trial to be completed. This new multi-component clinical trial design allows more efficient screening and facilitates the addition of new drugs and biomarkers into the protocol on a "rolling" basis.

Two types of studies follow this design: "Basket" studies which examine the effect of specific therapeutic agent(s) on a specific genetic or molecular biomarker regardless of the type or subtype of cancer in which it occurs. Patients with the different types of cancer are evaluated in separate sub-studies, or "baskets". This allows analysis of the responses to the therapy for each type of cancer

evaluated, as well as responses to the drug across cancer types. An example is the National Cancer Institute's Molecular Analysis for Therapy Choice (MATCH) trial. Lung-MAP is an example of the second type, "Umbrella" studies, which evaluate different therapy/biomarker combinations in a single type of cancer. Other examples are I-SPY 2 in breast cancer, Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination (BATTLE) in non-small cell lung cancer (which I co-led while at The University of Texas MD Anderson Cancer Center and now we have BATTLE-2 as an National Cancer Institute [NCI] funded program at Yale in collaboration with my colleague Dr. Vassiliki Papadimitrakopoulou at The University of Texas MD Anderson Cancer Center), and FOCUS4 in colorectal cancer. The unique aspect of Lung-MAP is that it will build on the principles and approaches of the previously mentioned trials, but for the first time, it will be an "umbrella" study conducted in a late phase setting (phase II/III) allowing successful drug candidates to be immediately considered for approval. This model can provide system wide benefit because phase III trials are often the largest, longest, and most expensive to conduct. Another distinctive feature of Lung-MAP is the ability for a drug that is found to be effective in phase II to move directly into the phase III registration components, incorporating the patients from phase II. This unique statistical approach can save both time and the number of patients that would be needed to program compared to conducting separate phase II and phase III studies.

The concept of the Lung-MAP was developed at the 2012 Friends of Cancer Research/Brookings Conference on Clinical Cancer Research and was initiated and opened in a year and a half. The goal is to develop a biologically driven approach – building on the NCI funded Cancer Genome Atlas (TCGA) to identify targets. In February 2012 the NCI, including investigators of the Thoracic Malignancy Steering Committee (TMSC), the Food and Drug Administration (FDA), European Medicines Agency (EMA), and pharmaceutical companies met together on the subject of "Strategies for Integrating Biomarkers into Clinical Development of New Therapies for Lung Cancer". Following that meeting, a TMSC task force

was established to develop a series of Master Lung Cancer Protocols chaired by Dr. Fred Hirsch at the University of Colorado. Prior to this and simultaneously, the Friends of Cancer Research (FOCR), let by Drs. Ellen Sigal and Jeff Allen in conjunction with FDA and NCI, initiated a similar effort presented as part of the 5th Annual Friends of Cancer Research/Brookings Institution Conference on Clinical Cancer Research in November 2012, which they asked me to chair. We published a white paper which was the basis for this trial. Finally in March 2013, at a follow-up FOCR Forum, the decision was made to go forward with the study now known as Lung-MAP, which is a public-private partnership involving the NCI and its Cooperative Group/National Clinical Trials Network (NCTN) infrastructure, the FDA, multiple pharmaceutical companies, FOCR, and lung cancer non-profits and patient advocates. The study is being executed by the Foundation for the National Institutes of Health (FNIH) and coordinated by the Southwest Oncology Group (SWOG).

Benefits of Lung-Map approach include:

- Enrollment Efficiency: Grouping these studies under a single trial reduces the overall screen failure rate
- Operational Efficiency: A single master protocol can be amended as needed as drugs enter and exit the study
- Cost Efficiency: As a result of shared services, utilization of existing infrastructure, and avoiding redundancy of processes, this public-private partnership will be operated at a cost substantially less than operating individual trials
- Consistency: Every drug entered into the trial would be tested in the identical manner
- Predictability: If pre-specified efficacy and safety criteria are met, the drug and accompanying companion diagnostic will be approved

- Transparency: All study activities are vetted and approved by a multi-stakeholder governance structure including an Oversight Committee and Drug Selection Committee
- Patient Benefit: offers the advantage of bringing safe and effective drugs to patients sooner than they might otherwise be available

Patients with advanced-stage lung squamous cell carcinoma whose disease has progressed on first-line therapy are assigned to a sub-study and then randomized within that sub-study to biomarker-driven targeted or standard-of-care (SOC) therapy. Our goal is to accrue 625 patients per year and to run 4–7 sub-studies concurrently. Sub-studies are defined by a genotypic alteration (biomarker) in the tumor and a drug that targets this alteration. Patients bearing more than one relevant biomarker are assigned to a sub-study based upon a pre-defined algorithm that helps facilitate even enrollment across all sub-studies. The protocol also includes a "non-match" sub-study for screened eligible patients that do not qualify for any of the current biomarker-driven sub-studies. This sub-study will compare a non-match therapy (which in the first iteration of Lung-MAP is an immunotherapy not yet shown to be effective in a limited, biomarker defined population) to SOC. A non-match sub-study will be open to accrual throughout the trial. Each sub-study will function autonomously and will open and close independently of the other sub-studies. Each sub-study is independently powered for overall survival (OS) with an interim analysis for progression-free survival (PFS) to determine the "go-no go" decision to proceed from phase II into phase III. Along with the paired biomarker, agents that are successful at interim analysis in phase II based on PFS will continue enrollment to evaluate phase III endpoints which include clinically meaningful increased PFS and OS for potential registration of the drug. Candidate drugs are evaluated by a multidisciplinary drug selection committee using specific criteria, such as:

- Demonstrated biologic activity against the target associated with a proposed predictive biomarker(s)
- Well-understood mechanism of activity against the target

- Evidence of clinical activity in cancer, particularly in squamous cell cancer (*e.g.*, phase I responders)
- Manageable toxicity as a monotherapy and in combination with chemotherapy
- Practical dosage regimens that are acceptable to the patient and clinician

Currently, the study team has been looking at single agents, but will begin to explore combinations of targeted drugs. Candidate biomarkers defined primarily as genetic alterations (mutations, amplifications, fusions) detected on a commercially available next generation sequencing (NGS) platform—Foundation 1. In some cases, *e.g.*, where over-expression is key to defining presence of actionable target, sequence-based screening will be supplemented by immunohistochemical assays or other methodologies as appropriate, performed in a Clinical Laboratory Improvement Amendment (CLIA)-approved setting.

There are challenges to the Lung-MAP approach, and to cancer drug development generally, that we believe can be addressed and can be a model for future trials. For one, it requires large and rapid accrual with many sites near patients, which we believe can in part be addressed by the new NCI NCTN mechanism. The NCTN coordinates activities between different cooperative group research sites and their affiliates, which will allow Lung-MAP to be offered as a clinical trial option at hundreds of sites around the country. In order to try and accelerate access to as many sites as possible, Lung-MAP utilized the recently established NCI Centralized IRB. By doing so, individual research institutions that allow the Centralized IRB to replace institutional IRBs reduce administrative steps to activating the trial, while maintaining the safety of study participants. With hundreds of sites activating Lung-MAP, having one main IRB review as opposed to hundreds can greatly accelerate the time in which the trial becomes available to patients.

Another challenge is that Lung-MAP requires commitment by pharmaceutical partners and the FDA to ensure that trial provides a regulatory approval pathway. To support this, we have involved all partners NCI, FDA, pharmaceutical companies, academic leaders, FOCR, and FNIH in the design and development of study as whole and individual sub-studies. Furthermore, it is difficult to conduct randomized trials in setting where patients have multiple options for obtaining treatment with targeted agents. In order to reduce confusion and help patients reach the best decisions for their care, we have implemented a system to provide guidance to physicians and patients on evaluation of screening results. In some cases, exciting new drugs may have too little supporting clinical data for selection for Lung-MAP. To address this, we are looking to establish a mechanism (*via* phase I/IIa studies) to seamlessly develop needed data for a new candidate to become eligible for Lung-MAP.

Finally, in many clinical trials it may be difficult to discern differences in how patients are feeling as a result of drug therapy. As Lung-MAP proceeds, the study is already examining ways that patient reported outcomes (PROs) could be incorporated into the study so that important improvements to patients' health quality can also be measured in additional to analyzing each drug's anti-cancer potential. By using Lung-MAP as a venue to validate a lung cancer PRO, the resulting metrics will become available for future lung cancer trials without having to keep developing and validate new methods each time.

Despite these challenges that will be addressed as the study progresses, there are many key benefits of the trial including;

- Grouping biomarker driven targeted drug studies under a single arm will reduce screen failure rate, making the screening worthwhile for both patients and physicians

- Operational and protocol development efficiencies of having a master protocol
- Consistency of applying a master protocol—every drug for the disease would be tested in the identical manner
- Regulatory approval pathway for drugs and companion diagnostic biomarker provided
- Shared infrastructure for screening, database, enrollment, *etc.* less costly than individual studies
- Improvement in overall efficiency of drug development in a specific disease setting, bringing safe and effective drugs to patients sooner than they might otherwise be available

In summary, we believe that Lung MAP, this unique public-private partnership, is a unique vehicle to both benefit patients and support accelerated research and drug approval. This has been a team effort with FOCR (led by Ellen Sigal and Jeff Allen), NCI (Jeff Abrams); SWOG (Vali Papadimitrakopoulou, David Gandara, Charles Blanke, Fred Hirsch, Mary Redman), FDA, and the private industry.

The potential of studies like Lung-MAP and other similar efforts is built on several key components that we believe this committee can consider as the 21st Century Cures Initiative advances:

- Biomarkers: Lung-MAP is systematically evaluating multiple genotypic markers within the same study to assess their impact in lung cancer and beyond. Studies that incorporate Biomarker evaluation are frequently far more expensive than traditional clinical trials. The 21st Century Cures Initiative could establish an increased rate of per patient reimbursement to support and incentivize these types of trials.

- Diagnostics: A framework is needed to help coordinate the development, validation, regulation, reimbursement, and implementation for advanced diagnostics. This is no small challenge. For

example, the NIH voluntary registry for genetic testing contains 19,000 tests for 4500 conditions. Lung-MAP will help provide a case study - but this is just one approach. This committee should consider developing a framework of policies governing advanced diagnostics, including the pre-market and post-market authorities for data generation and requirements and rates for reimbursement.

- Partnerships: Lung-MAP is an example of a multi-stakeholder partnership that has already been able to accelerate clinical trial processes and we are committed to continue to do so in many other ways as the study now moves forward. In order for more of these types of partnerships to occur, this committee could examine incentive structures and processes to facilitate data generation/sharing and collaboration. This could include the review of current administrative practices for establishing and implementing large scale trials to standardize approaches so future partnerships are building on past successes and not starting over.

- Resources: We do need to ask for more resources and funding to do more such projects. The NCI budget is flat at best and it is difficult to bring new drugs and profiling to patients. We therefore ask for sustained funding for NIH and FDA with a diminution of the constraints on education, travel and paper work that make these projects even more complicated.

Lung-MAP is a public-private collaboration where each sector has committed to committed to do business differently. Together we believe that Lung-MAP can demonstrate a new model for high-quality drug development in less time, at less cost, for more people, and most importantly, improve the lives of patients with lung cancer. The shared goal of accelerating the pace in which new drugs are developed is

the driving force behind this partnership. We know that this Committee shares that goal, and so we thank you for taking on this important 21st Century Cures Initiative.

Appendix – Lung-MAP Leadership & Committees:

Study Co-Principal Investigators

David Gandara, Director, Thoracic Oncology Program, UC Davis

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center

Fred Hirsch, Professor of Medicine and Pathology & Associate Director for International Programs
University of Colorado Cancer Center

Philip Mack, Assistant Adjunct Professor, Co-Leader Molecular Pharmacology, UC Davis Comprehensive Cancer Center

Vali Papadimitrakopoulou, Professor, Department of Thoracic/Head and Neck Medical Oncology, MD Anderson

Mary Redman, SWOG Statistical Center in Seattle & Fred Hutchinson Cancer Research Center

Lawrence Schwartz, Chair of Radiology, Columbia University & Chair of SWOG Imaging Committee

Lung-MAP Trial Oversight Committee

Roy Herbst, Chief of Medical Oncology, Yale Cancer Center (Co-Chair)

Ellen Sigal, Chairperson and Founder, Friends of Cancer Research (Co-Chair)

Jeff Abrams, Associate Director, NCI-CTEP

Charles Blanke, Group Chair, SWOG

Tony Coles, Former CEO, Onyx Pharmaceuticals

Gwen Fyfe, Former Vice President, Oncology Department, Genentech

David Gandara, Chair, Lung Committee, SWOG-UC Davis

Gary Gilliland, Dean and VP, Precision Medicine, University of Pennsylvania

Fred Hirsch, Professor of Medicine and Pathology & Associate Director for International Programs
University of Colorado Cancer Center

Gary Kelloff, Special Advisor, NCI-DCTD

Liz Mansfield, Director, Personalized Medicine, CDRH, FDA

Vali Papadimitrakopoulou, Professor, Department of Thoracic/Head and Neck Medical Oncology, SWOG-
MD Anderson

David Wholley, Executive Director, The Biomarkers Consortium, FNIH

Janet Woodcock, Director, CDER, FDA

Lung-MAP Drug Selection Committee

Roy Herbst, Associate Director, Translational Research, Yale (Chair)

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David Simpkins, MS, Vice President, Strategic Communications Planning, American Cancer Society

Scott Santarella, President and CEO, Addario Lung Cancer Foundation

Mr. PITTS. Chair thanks the gentleman.

And now recognize Dr. Khosla, 5 minutes for an opening statement.

STATEMENT OF SUNDEEP KHOSLA

Mr. KHOSLA. Good morning. My name is Sundeep Khosla. I am a practicing endocrinologist and Dean for Clinical and Translational Science at Mayo Clinic in Rochester, Minnesota. I am also the principal investigator at the Mayo Clinic Clinical and Translational Science Award, or CTSA, from the National Center For Advancing Translational Sciences, NCATS, at NIH. I salute the 21st Century Cures Initiative, and am please to share some thoughts on the opportunities and challenges we face in bringing new treatments to patients.

Mayo Clinic has facilities in six States and provides care for more than 1 million people annually from all 50 States and 135 countries around the globe. In addition to clinical care, Mayo has a robust research program, including clinical trials. Over the years, Mayo has conducted pivotal clinical trials in many areas, including diabetes, osteoporosis, heart disease, and cancer. Mayo Clinic won a Nobel Prize in Physiology and Medicine in 1950 for the discovery of cortisone and its clinical applications. Conducting clinical trials is an extremely high priority for Mayo.

With the Congressional investment in NIH over the past several decades and the NIH-supported human genome project, we are now in a truly exciting era where there are more possibilities for understanding diseases and developing new drugs and new treatments than ever before.

With these opportunities, however, have come significant challenges. To address these challenges, NIH Director Collins created NCATS in December 2011 to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementations of interventions that tangibly improve human health across a wide range of human diseases and conditions.

As astutely recognized by this committee, the clinical trials process needs modernization. NCATS is seeking to do just that by funding CTSAs at 62 sites around the country, thus essentially creating a network of potential clinical trial sites. The vision is that high priority clinical trials funded either by NIH or by industry could be run very efficiently through all or part of the 62-site network.

While implementation is not easy, there are three changes that would facilitate the work of the NCATS clinical trials network. One is institutional review board, or IRB reciprocity, between as many of the sites as possible. Because each institution has its own IRB, there are frequent and often lengthy delays in multi-center clinical trials as each IRB reviews and eventually approves a clinical trial protocol.

Reciprocity between as many sites as possible would mean that once the IRB at the primary site approved the protocol, that approval would be accepted by the remaining sites.

Second, there needs to be much greater interoperability of electronic health records. This could allow, for example, study inves-

tigators to rapidly search for study participants across all 62 CTSA sites.

Third, for a national network of clinical trial sites to truly function efficiently, there needs to be greater harmonization of regulations. For example, an investigator today must contend with different regulatory requirements from the Office for Human Research Protections, the FDA, and the Office for Civil Rights, all within HHS. Further complexity is added by State laws that may go beyond the Federal requirements.

What can Congress do to help facilitate clinical trials at the national level? I have four suggestions:

First, continue to support the efforts of NCATS and the CTSAs through ongoing and, if possible, enhanced funding.

Second, help develop policies that encourage IRBs to have greater reciprocity with other institutions.

Third, urge HHS to accelerate progress towards interoperability of electronic health records.

Finally, develop policies for greater harmonization of regulations across Federal agencies and across States.

Responsibility for modernizing clinical trials falls also on the shoulders of individual academic medical centers. Here are three ideas academic medical centers could consider to modernize clinical trials:

One, work to shorten the time required for study initiation through more streamlined contract negotiation with industry and for IRB approval.

Two, because disagreements over the use of biospecimens often cause considerable clinical trial delay, work to develop a simplified biospecimens policy that is broadly accepted across sites and companies.

Third, develop better electronic capabilities to enhance recruitment, screening, enrollment, and tracking of study participants.

In summary, the opportunities for bringing new treatments to patients have never been greater, yet significant challenges remain. Congress can help this effort by supporting discovery science, NCATS, and the CTSA system, and by removing roadblocks in the clinical trials process. Together Government, the private sector, and academic medical centers must all step up and do all we can to rapidly deliver discoveries to the people who need them.

Thank you for your opportunity to testify today.

[The prepared statement of Mr. Khosla follows:]

MAYO CLINIC

Hearing on "21st Century Cures: Modernizing Clinical Trials"

Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

Testimony of:

Sundeep Khosla, M.D.
Dean for Clinical and Translational Science
Mayo Clinic
Rochester, Minnesota

July 9, 2014

MAYO
CLINIC

Introduction

Good afternoon Chairman Pitts, Representative Pallone and distinguished members of the House Energy and Commerce Health Subcommittee. My name is Sundeep Khosla, M.D., and I serve as the Dean for Clinical and Translational Science at Mayo Clinic in Rochester, Minnesota. I also am the principal investigator of the Mayo Clinic Clinical and Translational Science Award (CTSA) from the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH). I salute the 21st Century Cures initiative of this Committee, and in the brief time allocated to me, I would like to summarize Mayo Clinic's perspective on the current status of the conduct of clinical trials in the United States and the tremendous opportunities, as well as significant challenges, we face for bringing new treatments to our patients.

Mayo Clinic Background on Research and Clinical Trials

Mayo Clinic is a not-for-profit health care system dedicated to medical care, research, and education. With more than 3,600 physicians and 60,000 employees, Mayo Clinic demonstrates a relentless and unwavering commitment to excellence, which has spawned a rich history of health care innovation. The Mayo Clinic logo of three interlocking shields symbolizes Mayo's commitment to excellence and interdependence in the three areas of Research, Education and Clinical Practice.

Mayo Clinic, which has facilities in six states, provides care for more than one million people annually from all 50 states and 135 countries around the globe. This year, we are celebrating our 150th anniversary as an institution, and throughout our history, the needs of the patient have always come first. In addition to clinical care, this includes conducting both laboratory-based and clinical research, including clinical trials. Indeed, as stated so eloquently by Dr. William Mayo, "The research we do today will determine the type of medical and surgical practice we carry on at the clinic tomorrow." Perhaps the most dramatic example of this commitment to research is the discovery of cortisone in the 1930s by Dr. Edward Kendall and his subsequent partnership with a clinician who saw patients with arthritis, Dr. Phillip Hench, leading them to test cortisone clinically in a patient in 1948. The rest is history, including the awarding of the Nobel Prize in Physiology and Medicine to Drs. Kendall and Hench in 1950. Since then, Mayo Clinic has played a critical role in pivotal clinical trials in many areas, including the treatment of diabetes, osteoporosis, heart disease and cancer. Mayo Clinic also had identified clinical trials as an extremely high priority for Mayo research.

Future of Clinical Trials

It is safe to say that with the investment in discovery science at academic medical centers throughout the country by the NIH over the past several decades, we are now in an era where there are more possibilities for understanding disease pathways and developing new drugs than ever before. These are truly exhilarating and exciting times to be a scientist involved in biomedical research. Thanks in large part to the NIH-supported human genome project, there are now literally thousands of new potential drug targets, and patients with many serious diseases

have the right to have real hope that cures for their diseases may be achievable in their lifetimes. With these opportunities, however, come significant challenges. Perhaps the biggest of these is what has come to be called by many the translational "Valley of Death." This refers to the fact that the average length of time from target discovery to approval of a new drug currently averages approximately 14 years, the failure rate exceeds 95%, and the cost per successful drug exceeds $2 billion, after adjusting for all of the failures.

To address these challenges, Dr. Francis Collins (NIH Director) created the National Center for Advancing Translational Sciences (NCATS) in December 2011. The mission of NCATS is "To catalyze the generation of innovative methods and technologies that will enhance the development, testing and implementation of interventions that tangibly improve human health across a wide range of human diseases and conditions." Largely through the Clinical and Translational Science Awards (CTSAs), NCATS is pursuing this goal at multiple levels, including facilitating new drug discovery, providing the tools to better understand human physiology and disease, discovering new biomarkers, and most relevant to the discussion today, enhancing the conduct of clinical trials.

As astutely recognized by this Committee, the clinical trials process in the US, and indeed around the world, needs to be modernized. At a national level, NCATS is doing this by funding CTSAs at 62 sites around the country, thereby essentially creating a network of potential clinical trial sites. Thus, the vision is that high priority clinical trials, funded either by NIH or by industry, could be run very efficiently through all or part of this network. However, this is clearly not as easy as it sounds.

First, each institution currently has its own Institutional Review Board (IRB) that reviews human studies, and there are routinely considerable delays in multi-center clinical trials as each IRB reviews and eventually approves a clinical trial protocol. Additional delays are encountered when modifications are made to a clinical trial, leading each site IRB to review those modifications. A goal that the CTSA network is pursuing is to have IRB reciprocity between as many sites as possible, and potentially all 62 sites, so once the IRB at the primary study site approves the protocol, that approval is accepted by the remaining sites. This "IRB reliance" model is currently being rolled out through multiple CTSA sites and has the potential to significantly accelerate the conduct of multi-site clinical trials.

Second, there needs to be much greater interoperability of the electronic health records. This could facilitate, for example, a study investigator's search across all 62 CTSA sites and beyond for the potential pool of study participants at various centers, which – with appropriate privacy protections – could allow her/him to select the ones where the study could be most rapidly conducted. While not the topic for today, interoperability is also critical for other types of outcomes research, including comparative-effectiveness research in real work clinical practice.

Third, for a national network of clinical trial sites to truly function efficiently, there needs to be greater harmonization of regulations across federal agencies and across states. Just as an example, an investigator today has to deal with somewhat different regulatory requirements from the Office for Human Research Protections (OHRP) (Common Rule), the Food and Drug Administration (FDA), and the Office for Civil Rights (Health Insurance Portability and

Accountability Act [HIPAA]) privacy rules. Superimposed on this are individual state requirements.

How Congress Can Help

What can Congress do to help facilitate clinical trials at the national level? First, continue to support the efforts of NCATS and the CTSAs through ongoing and, if possible, enhanced funding. As summarized by the June 2013 Institute of Medicine (IOM) report on the CTSA program, "The IOM Committee found that the CTSA program is contributing significantly to advancing clinical and translational research," although they did recommend "a number of revisions to make the program more efficient and effective and to ensure its future success." Second, help develop policies that encourage IRBs to have greater reciprocity with other institutions and thereby avoid duplicating efforts multiple times for a given clinical trial. Third, provide funding and incentives for developing greater interoperability of medical records across the country. Finally, develop policies for greater harmonization of regulations across federal agencies and across states.

The responsibility for modernizing clinical trials falls also, however, to the individual academic medical centers. Each step in the clinical trial process needs to be closely examined and potentially modified. Prior to study activation, the time required for contract negotiation with industry and IRB approval should be made as short as possible. The use of "master agreements" between academic medical centers and companies, as well as greater IRB reciprocity (as noted above), would greatly facilitate relieving this bottleneck. An additional issue that often causes considerable delays is disagreements between the medical center and the industry sponsor

regarding the use of biospecimens; having a more streamlined biospecimens policy that is broadly accepted across sites and companies would be of tremendous value. There also needs to be a greater feasibility assessment for subject recruitment at each site in order to avoid initiating studies that are doomed to fail at that site.

Following activation of the clinical trial, there is a need for better electronic capabilities to enhance recruitment, screening, enrollment and tracking of study participants. There also is a tremendous need to train young clinicians in the conduct of clinical trials in order to have both a robust cadre of clinical trialists as well as a pipeline for future clinical trialists. Finally, many institutions struggle with having sufficient ethnic and racial diversity in a given clinical trial, and ways to enhance the participation of minorities in clinical trials are clearly needed. This also has been a problem in terms of representation of women in trials. While many of these issues are local to each academic medical center, Congress can help by providing incentives to enhance the ability of the medical centers to streamline their clinical trial process. It is only through a concerted national and local effort that the problem of modernizing clinical trials can be adequately addressed.

Industry also must play a role in modernizing clinical trials, in partnership with academia and regulatory agencies. The current clinical trial model of a placebo-controlled, randomized, double-blinded clinical trial may not be the most effective model, particularly for early phase studies. Thus, there is growing interest in alternate clinical trial designs, including "adaptive trials," which aim to use the information generated in the trial as it emerges, not simply when the study has been completed. As an example, by pre-specifying analyses to be conducted during the

trial, subjects could be allocated to drug doses that show the greatest benefit early on, thereby exposing fewer patients to ineffective doses, resulting in more ethical treatment of patients. Importantly, the FDA has published guidance on the appropriate use of adaptive clinical trial designs. However, there needs to be ongoing dialog between pharma, academia and the FDA in developing more creative, and yet scientifically rigorous, methods to conduct clinical trials more efficiently. In short, the science of clinical trial design needs to continue to advance, and this should be facilitated by the FDA and other regulatory agencies.

Conclusion

In summary, the opportunities for bringing new drugs to patients have never been greater, but significant challenges remain. Congress can, and should, help this effort through continuing and enhancing support for discover science, NCATS, and the CTSA system. Legislative policy changes and incentives are necessary to remove specific roadblocks in the clinical trials process. Together, government, the private sector, and academic medical centers must all step up and do all we can to rapidly deliver discoveries to our patients.

MAYO CLINIC

About Mayo Clinic:

Mayo Clinic is the first and largest integrated, not-for-profit medical group practice in the world. Doctors from every medical specialty work together to care for patients, joined by common systems and a philosophy that the needs of the patient come first. 4,100 physicians and scientists and 53,600 allied health staff work a Mayo which has campuses in Rochester, Minn.; Jacksonville, Fla.; and Phoenix/Scottsdale, Ariz. Mayo Clinic also serves more than 70 communities in the Upper Midwest and Georgia through Mayo Clinic Health System. Collectively, these locations care for more than 1.1 million people each year. Mayo Clinic is governed by a Board of Trustees composed of public members and Mayo physicians and administrators.

Mayo Clinic's mission is to inspire home and contribute to health and well-being by providing the best care to every patient through integrated clinical practice, education, and research.

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Mr. PITTS. Chair thanks the gentleman.

And now recognize Ms. Stafford, 5 minutes for an opening statement.

STATEMENT OF PAULA BROWN STAFFORD

Ms. STAFFORD. Good morning, Chairman Pitts, Ranking Member Pallone.

Mr. PITTS. Make sure your button is pressed. Thank you.

Ms. STAFFORD. Good morning, Chairman Pitts, Ranking Member Pallone, and members of the Health Subcommittee. Thank you for the opportunity to appear before you today. My name is Paula Brown Stafford. I am president of Clinical Development at Quintiles, the world's largest provider of biopharmaceutical development and commercialization services. We have more than 29,000 employees globally, including nearly 10,000 here in the U.S. We are engaged every day in helping bring better medicines to patients faster.

To give you a sense of our scope, over the past 10 years, we have enrolled nearly 1 million patients in clinical trials at over 100,000 investigative sites like Yale, Mayo Clinic.

Our experience and our role as a facilitator of the process gives us a unique vantage point on where the challenges and opportunities are in the drug development process.

We all agree the development process is too expensive, in excess of a billion per NME, and takes too long. Generally, that is 7 to 10 years. And, yes, patients are waiting.

Modernizing clinical trials is critical if we are to meet the goals we share of delivering medicines faster at less cost to patients who need them.

Quintiles works closely with our biopharma customers and the FDA to find better ways to design and execute studies to meet this goal, and we have had many collaborative successes to date, yet there is more to be done.

My remarks will focus on three areas for further innovation and a number of recommendations where Congress can help accelerate meaningful improvements.

First, with nearly 80 percent of total drug development time and cost spent on clinical trials, we must focus on patients, creating better ways to find the right patients for the right clinical trials. The bulk of time to conduct a clinical trial is spent in finding patients that meet the increasingly complex inclusion/exclusion criteria of trials today. Improving data collection and accessibility would facilitate more rapid identification of patients suitable for clinical trials. Without new approaches and better access to data, patient recruitment will become increasingly difficult, especially as we work to develop cures that are more targeted or personalized based on genomics.

Second, there is much more room for improving the process of conducting clinical trials, reducing the timeline for each trial by eliminating redundancies and inefficiencies, particularly in what is known as the startup phase, where it can take up to 18 months just to get to a point where a study is open for patient enrollment.

Also standardization of clinical trials. The protocols, the data collection requirements would help to reduce repetitive activities that happen across trials.

Among private sectors, the Clinical Data Interchange Standards Consortium, CDISC group I chaired from 2012 to 2011, has recently even created data standards for a number of therapeutic areas, including multiple sclerosis, Alzheimer's, and asthma.

The third area is pathways. Alternative development pathways could speed the introduction of new therapies to address serious unmet medical needs as an alternative to the traditional three-phase clinical trial paradigm. Great strides have been made by the passage of FDASIA—the anniversary is today, 2 years ago today. Also the creation of the breakthrough therapy designation and other expedited drug approval pathways. However, these have largely addressed FDA review time, which was 10 months, but not the much longer development time, which is 10 years.

So how can Congress help? A number of recommendations.

One, Congress could encourage the FDA to set goals for more frequent use of master protocols and adaptive designs. Both of these approaches allow multiple drugs to be evaluated in the same trial, identify affected and non-affected populations faster. And Quintiles has recently submitted a proposed master protocol for diabetes, CVOT, to the FDA, and are expecting comments later this month.

Congress could take steps to improve the quality and accessibility of the data to researchers and thereby improve the speed and accuracy of identifying the right patients for the right trial. Among these steps are incremental improvements to linkages between EHR and clinical research databases, better interoperability among EHRs, and examining where there are misinterpretations of HIPAA and other data privacy regulations that may be inadvertently hampering the use of de-identified data to improve research.

Congress should explore ways that the FDA and the NIH could encourage the use of central IRBs, which, in our experience, can cut the time to even start an individual investigative site for more than 100 to 45 days.

And Congress could encourage FDA to pilot alternative development pathways, similar to the adaptive licensing approach that the EMA is now piloting. The tools and science are in place to support alternatives whereby treatments could be tested and approved for limited use while ongoing studies would still be required.

Chairman Pitts, members of the subcommittee, I ask you and your colleagues to support these recommendations because at the end of the day a spouse, family member, a friend, or even you may benefit from the next drug discovery that a modernized clinical trial system brings forth.

Thank you.

[The prepared statement of Ms. Stafford follows:]

QUINTILES

Statement of Paula Brown Stafford
President – Clinical Development
Quintiles

Before the Committee on Energy and Commerce
Subcommittee on Health Hearing On

"21st Century Cures: Modernizing Clinical Trials"

July 9, 2014

Good morning, Chairman Pitts and Ranking Member Pallone, and members of the Health Subcommittee; thank you for the opportunity to appear before you today and to add to the 21st Century Cures Conversation.

My name is Paula Brown Stafford; I am President of Clinical Development at Quintiles, the world's largest provider of biopharmaceutical development and commercialization services, with more than 29,000 employees globally, including nearly 10,000 in the U.S. Together we deliver services in over 100 countries and are engaged every day in helping bring better medicines to patients faster. To give you a sense of our scope, over the past 10 years, we have enrolled nearly 1M patients in clinical trials at over 100,000 investigative sites. We are pleased to be part of today's hearing on Modernizing Clinical Trials.

The breadth and depth of our experience, as well as our role as a facilitator of the process, gives us a unique vantage point on where the challenges - and opportunities - are in the drug development process. It is a process we all agree is too expensive (in excess of $1 billion) and that takes too long – generally seven to 10 years. At the end, as we all know – patients are waiting.

Modernizing clinical trials is critical if we are to meet the goals we share of delivering better medicines faster, at less cost, to patients who need them. The biopharma industry and its service providers, along with FDA and other stakeholders have made great strides in improving the process. We work closely with our customers and the FDA to find better ways to design and execute studies to meet this goal, and have had many successes and appreciate the spirit of collaboration from the FDA. Nonetheless, more can be done.

My oral testimony will focus on three areas for further innovation and then offer a few of the suggestions of where Congress could help accelerate meaningful improvements.

1. Utilizing newer design approaches and improving data accessibility to improve our focus on **patients**, creating better ways to find the right patients for the right clinical trials;
2. Modernizing the **processes** of drug development, including ways to improve the quality and efficiency of clinical trials, reducing the timeline for each trial by eliminating redundancies and inefficiencies
3. Establishing alternative development **pathways** to speed the introduction of new therapies to address unmet medical needs.

In this written testimony, we provide a more comprehensive exploration of these areas, provide the rationale for solutions and make additional recommendations.

<u>Master Protocols and Adaptive Designs to Target Therapies to the Right Patients, Efficiently</u>

<u>The Challenge</u>

Clinical trial productivity is dramatically reduced and costs are vastly increased by the need for each Sponsor to conduct separate development programs in the same patient population for the same indications, for similar molecules or for molecules with common pharmacological mechanisms of action.

Drug development failure rates are high, time is wasted with duplicative recruitment and other efforts, and patient participation is not optimized.

A Solution

Various study design approaches that identify failures faster and advance promising drugs are available, including Adaptive Designs and Master Protocols.

Adaptive Trial Design: There are many types of adaptive designs, but all such designs use Bayesian methodology to characterize drug efficacy more precisely and efficiently in selected populations, based upon cumulative experience. It is also possible to combine adaptive design within Master Protocols, such that multiple drugs can be simultaneously evaluated, such drugs "rolling in" or "rolling off" as available for study and as evaluation is completed. This approach is currently being evaluated for wider adoption by the EMA. The national regulatory authority in Singapore has similarly investigated the use of adaptive authorization within Master Protocols.

Master Protocols: A Master Protocol allows multiple drugs to be evaluated in the same trial, with inclusion criteria that are relatively homogenous, and any necessary customization based on drug characteristics. Multiple compounds for a particular indication can be tested within the same Master Protocol, rather than requiring a separate protocol/development program for each. Only one placebo-controlled arm would be required instead of duplicating the same arm for each drug. This standardized, progressive regulatory approach would require fewer patients be on placebo and fewer enrolled overall, and significantly reduce costs and timelines by not requiring separate start-up and recruitment processes for different therapies.

The I-SPY 2 trial is an example of an adaptive trial using a Master Protocol, being carried out by a consortium involving industry and academia, with the collaboration of the FDA. I-SPY 2 takes an agile

approach, using a Master Protocol in which multiple oncology agents are evaluated in similar populations, with predefined success criteria, using a Bayesian adaptive design. The trial is for women with newly diagnosed locally advanced breast cancer segregated into treatment arms based upon biomarkers and other criteria. The study is evaluating whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone before having surgery, using complete radiographic response/remission, rather than event-free survival as the efficacy endpoint. The trial is simultaneously testing multiple investigational drugs thought to target the biology of each participant's tumor. If the data is supportive that a particular drug is may prove effective in a given patient subpopulation, this "proof of concept" study can form the basis for a subsequent Phase III trial, in which confirmation of response on this same radiographic endpoint can form the statutory basis for approval. The Sponsor must, however, commit to continuing the trial in order to assess the effects of the drug on event-free survival and to obtain broader labelling claims. Dr. King Jolly, Senior VP of Quintiles, serves as a member of the Executive Steering Committee of this trial, and has helped formulate operational, scientific, and regulatory strategies related to this program. Quintiles is also providing the traditional Clinical Research Organization (CRO) services for this trial, and has provided financial support.

Recommended Approach

Quintiles recommends encouraging the use of adaptive designs and Master Protocols to maximize identification of drugs that work in the patient population without having to duplicate efforts across multiple Sponsors. Congress could consider requiring a certain percentage (perhaps 10%) of therapies entering Phase II to include Master Protocols and adaptive designs and that regulatory standards and approval criteria be clarified to encourage multiple biopharma companies to collaborate on Master Protocols with Bayesian designs.

Using Data to Facilitate Better Clinical Trials and to Benefit Patients

The Challenge

The practice of medicine and evaluation of therapies is a continual process that has largely been an experience- and paper-based endeavour. Today's technologies offer greater opportunities to harness real-world data and perform advanced analytics to inform better medical decisions, identify new uses and cures, improve drug development timelines and success rates, and more. While there are many efforts and advances, more can be done to truly harness this value.

As the 21st Century Cures white paper points out, analyzing data from the delivery setting could improve Discovery, Development and Delivery of better treatments. Below are examples of the benefits of data analytics across the spectrum. Each of these is conducted today in varying degrees, but the accuracy and power of the insights are only as good as the data available for analysis:

Real World Data Drives Discovery	**Real World Data Improves Development**	**Real World Data Improves Delivery Decisions**
Improve understanding of disease and inform the next generation of development by identifying unmet needs and opportunities	Inform better study design, dosing, inclusion/exclusion criteria	Discover potential safety and interaction issues of approved therapies (which supports more aggressive approvals)
Identify new uses of approved therapies and support product extensions	Accelerate trial execution through integration with EMRs, with collection of data at point of care	Continually assess benefits and risks to inform better coverage and medical care decisions that reward value (cost *and* effectiveness)
	Accelerate patient recruitment through EMRs, social media, and internet-enabled patient portals that facilitate more rapid identification of patients suitable for clinical trials.	

A Solution

To achieve these benefits, public and private entities alike must continue to enable the evolution of clinical trial design and conduct from the traditional "analog and local" model to a "digital and global" one. This includes continued investment in technologies, expedited validation and use of new tools, and importantly, improved collection and accessibility of data.

In the **analog and local model** that is largely still the norm today, design and planning are based on individual experience, with patient recruitment depending on individual relationships. Finding the right patient is rather a hit and miss affair. Clinical trials are conducted with separate paper report forms that require duplicate entry of each visit (data in the clinician's usual patient care notes and then in clinical trial records) and rigid schedules. Before the adoption of electronic databases and analytics, interim data were not available for months at a time, and with conclusions drawn after biostatisticians combed through spreadsheets. Safety is demonstrated only through a large number of patients enrolled in studies. Clinical development programs are determined based upon regulatory precedent, the guidance from Key Opinion Leaders, and the experience of treating physicians.

In contrast, in a **digital, global model**, which the industry is making some small strides toward, design is informed by real-world large, de-identified datasets and performance and productivity metrics, with patient recruitment taking advantage of the Internet and social media. The right patient would be identified by prescreening through data collection instruments served through the Internet, and trials would be conducted by collecting data directly from EMRs or through data collected at point of care that is integrated with EMRs. Data would then be housed within HIPAA-compliant e-Source archives, accessible for real-time access, remote monitoring, and application of signal detection analytics to allow

"just-in-time" assessment of safety and protocol compliance. Interim data would be available within hours, and safety demonstrated through immediate access to real-world data. Clinical development, in effect, would be EMR-enabled.

Recommended Approach

To maximize benefits of technology and analytics to further public health there are varying steps Congress could take to improve the quality and accessibility of data, listed below in order from ideal to step-wise improvements:

Create a central repository of accessible securely de-identified patient-level data and make available for research use through appropriate licensing. This would speed discoveries and development and improve assessment of real-world safety in larger populations. It would be a bold step, but others – such as the UK National Health Service – have made this a public health priority, and are gaining benefits from data that have been adequately anonymized and 'de-risked.' Currently, there are many large stores of patient data that can be de-identified, but the risk of being associated with, or liable for, the re-identification of individual patients hampers the willingness of care networks to share data with external researchers and causes reluctance among sponsors to work with third parties to tap the data. There is a need for a source of de-identified patient data to allow outcomes to be tracked, allowing use of real-world post-marketing data to answer regulatory approval questions. Regulatory changes could be made to provide a safe harbor for use of de-identified real-world patient data.

Other steps that could lead to improvements, short of the central repository described above, include:

Unique Patient Identifiers: Unique, HIPAA-compliant patient identifiers that follow individuals across settings, care networks, multiple EMR and health information systems would enable more accurate and comprehensive tracking of treatment outcomes and disease prevalence, which would help post-

marketing surveillance, inform treatment options, identify treatment gaps and provide information to improve new drug development and clinical trial design and recruitment. At present, patient records and outcomes data may appear in many different places – including records from hospitals, pharmacies, ambulatory care centers, and death certificates – making accurate assessment of outcomes unattainable. A unique patient identifier would allow for easy decoupling of patients' identities and their record, protect privacy and reduce the disjointed nature of current systems and the duplication of identifying and de-identifying data as it is cleaned for research use.

Integration of EMRs: All EMR systems in the U.S. should ideally be interoperable to allow a free flow of longitudinal health data accessible by everyone. This would allow real-world outcomes to be discerned much more quickly, allowing risk/benefit assessment to be carried out on millions of patients in near real time. This would transform the way we do clinical trials, giving access to patient data from all sources – doctor's office, urgent care, pharmacy clinics, hospitals, secondary, tertiary care centers – allowing complete tracking of patient care and outcomes. The Partnership to Advance Clinical electronic Research (PACeR) initiative[1] is aiming to standardize data across multiple EMR systems, and to implement clinical trial data collection systems that "wrap around" EMRs, allowing continuity of care across all locations. CDISC has an initiative underway in this area and is a member of PACeR. The government of Singapore has a mostly-uniform, countrywide uniform EMR system with a lot of interoperability, allowing comprehensive assessment of safety data and outcomes. This has given the regulatory authorities the confidence needed to approve products for narrowly defined populations from smaller trials, followed by additional, larger trials to expand the label (adaptive or staggered licensing/approval).

[1] http://pacerhealth.org

Improved Data Standards/Integration to unlock the power of real-world late phase data: Improved data standardization and integration is needed, as is the ability to contact patients directly via digital communities. There is scope for standardization of Electronic Data Capture (EDC) formats, which at present are different in each company. Standards should be established for data that are gathered iteratively and are common to every trial, such as safety, demographics, pharmacokinetics and clinical pharmacology, and in some cases, therapeutic standards. EMRs are most useful in integrated delivery systems. In the U.S., there are many different EMR vendors/systems, and they are used in various permutations. For the most part, such systems are not interchangeable; nor are they configured for clinical trials. Quintiles has put together the COMPASS Distributed Data Network[2] of around 10 EMR systems covering 19 million people for studies, and this is proving useful for safety and outcomes research. Another useful approach is to carry out hybrid studies using de-identified data from EMRs, supplemented by more focused data collection the physician and the patient. This approach allows better clinical trial functionality from EMRs. Safety and adverse event (AE) reporting could be stimulated using an add-on patch to the EMR, giving the physician the option to report that a symptom may be related to a drug; if yes, a link could pop up to MedWatch.

Use of Social Media and the Internet in Drug Development: Social media has changed the doctor-patient relationship and is fuelling the rise of patient empowerment. Online communities for sharing of information about disease symptoms, medication side-effects and clinical outcomes have become commonplace. Many entrepreneurs and established companies – and the government – are leveraging these networks to inform their development strategies, and even to identify and recruit patients. For example, Quintiles' Mediguard.org and ClinicalResearch.com support a community of patients who have opted to provide medication and condition information and are motivated to participate in research.

[2] http://www.quintiles.com/assets/0/111/118/233/1338/d098e5fb-d882-475d-b305-8865c2131aae.pdf

Currently, over 2.6 million patients in the U.S., UK, France, Germany, Spain, and Australia have registered making it one of the largest and fastest-growing healthcare communities in history. Social media-based interactions of this kind represent a disruptive technology that can harness large, de-identified datasets. There is potential for a new research paradigm for data collection, adverse event reporting and even direct-to-patient recruiting for clinical trials, and social-media based trials. Potential benefits for clinical trials are far-reaching, including lower cost and high speed versus traditional site-centric model, better connectivity between multiple healthcare stakeholders, reduction of geographical limits, and the potential for long-term contact and participation.

Looking ahead, social media could accelerate timelines and reduce the costs of drug development in some diseases, with the potential to contact motivated patients directly, rather than working through the complexities and expenses of site contracting. The advent of a social media based trial is not unthinkable, and this is a truly disruptive force in healthcare. As with traditional trials, though, high data quality will be essential. The policy issue for today is to ensure adequate data protection and patient safety – including provisions for informed consent – without 'handcuffing' patients' ability to 'opt in' to research in the public forum of the Internet. Congress needs to protect such clinical trial participants from discrimination or other harms based on what they reveal online. The fact that pre-existing condition exclusions for health insurance are now prohibited is a step in the right direction.

Sharing of Precompetitive Data: It would be helpful if precompetitive data of no direct commercial value – including placebo data, safety and other data, data related to products that have failed and are no longer being developed, and data on products that are off patent – could be made available for modelling and simulation of trial outcomes. This could improve the probability of trial success for all

Sponsors. For example, under the new openFDA initiative the FDA is making public millions of reports about prescription medicines, such as adverse events and medication errors, between 2004 and 2013. The FDA has also done some work to encourage companies to submit genomic data associated with their early development programs to add to the general body of knowledge. More data would allow validation of additional tools.

Each of these approaches would help in varying degrees to improve the quality and availability of data, and would in turn improve discovery, development and delivery of new cures and improved treatments for patients. With the data and analytical tools available today, we already see the value in terms of improving design, predictability and achievement of patient enrolment and ultimately improving probability of success. In the post-marketing phase, as data and techniques improve, there is tremendous potential for insights to improve care, identify new uses and assure safety. Congress should work to encourage the integration and accessibility of data, within the bounds of patient privacy.

Improving the Processes of Drug Development

Reducing Today's Clinical Trial Timelines

The Challenge

It is well documented that clinical trials are taking longer, and are becoming more complex and thus more expensive. The entire site start-up process, from Ethics Committee/Institutional Review Board (IRB) approval through site contracting can take up to 18 months. This must be completed before recruitment may begin. Ethics Committee approvals are a major delaying factor in clinical trial start-up; it can take up to a year to get approval to use a site, such as a hospital or medical practice. At present, for a 200-site study, the protocol is typically reviewed 200 times (once by each site) and 200 contracts are separately negotiated. The fastest timelines Quintiles typically sees for centralized IRBs are 45 days

to approval vs. 105 days each with local, individual IRBs. Other factors delaying start up include not enough standardized clinical trial documentation, which leads to 'reinventing the wheel' for each study and often each site and the fact that there is currently much duplication of effort in regulatory filings, and sometimes trial criteria, between the United States and the EU.

Solutions

Below are short-term pragmatic solutions that would help improve trial timelines and reduce unnecessary duplication of effort and thus cost:

Centralized Ethics Committee Approvals: Our experience shows that central IRBs, whose job is to perform this function, are two to three times faster at providing protocol review and approval to proceed.

Recommended Approach: Congress should urge the FDA to strongly encourage the use of central IRBs for the initial protocol review at the IND (investigational new drug) approval meeting – so that once a protocol has been approved by a recognized central IRB, it would effectively be approved for any site in the United States. Subsequent reviews at the site level IRB would focus on the specific requirements of each individual site (local regulations, and factors related to patients and investigators), but would not revisit the protocol and hold up the initiation of the other activities needed to get the trial up and running. Centralized IRBs are already used successfully in Europe, and a centralized process has also been implemented in hospitals in Quebec, including templates for informed consent paperwork.

Standardization of Clinical Trial Data and Documentation Requirements: Standardizing clinical trial data and documentation requirements, including qualifications for sites and IRB approvals, and informed consent forms would expedite the site start-up timeline. Investigator contract negotiation is also a time-consuming process with scope for added efficiencies. In Europe and other regions, these

forms are approved by the regulatory authority as part of the clinical trial protocol review, with only minor changes being made at the site level.

Recommended approach: Congress should encourage the adoption of a harmonized set of standards that would result in a process that is less expensive and more iterative, making use of electronic systems and decreasing the paperwork involved. There are existing models and options that could be built upon to expedite this process, including collaborative private-sector efforts in the U.S. and approaches in other countries. The Clinical Data Interchange Standards Consortium (CDISC), an organization Quintiles helped found and which I previously chaired, has established widely-regarded standards to support the acquisition, exchange, submission and archive of clinical research data and metadata.

Establishing Alternative Development Pathways

The Challenge

It currently takes an average of over seven years of total development time for New Molecular Entities,[3] including large, expensive Phase III studies required to demonstrate safety and efficacy in a broad population. This does not include the consideration that the risk/benefit relationship can differ sharply depending on the severity of the patient's illness and the availability of alternative therapies. Therapies that could benefit smaller subsets of populations take longer to develop in today's model and face the prospect of not reaching those specific patients because of the 'up or down' determination of safety and efficacy for the broader population.

The creation of the Breakthrough Therapy designation and expedited drug *approval* pathways is a welcome advancement, and we applaud the effort, including use of surrogate endpoints, early consultation for more efficient trial design, the increasing use of biomarkers, etc. However, the actual

[3] http://csdd.tufts.edu/files/uploads/Outlook-2013.pdf

time savings offered focuses largely on FDA review time (reducing from average of 10 months to six) versus providing a condensed *development* timeline, which currently ranges from 5-10 years to advance through the three-phase model.

A Solution

Quintiles strongly supports the adoption of alternative development pathways to speed the introduction of new therapies that would address unmet medical needs for patients with serious or life-threatening conditions. An example of this is the Adaptive Licensing approach that the European Medicines Agency (EMA) is now piloting.[4] In 2013, a similar alternative pathway approach was the subject of an FDA public hearing.[5] Under the FDA proposal, "the drug's safety and effectiveness would be studied in a smaller subpopulation of patients with more serious manifestations of a condition. Such a pathway could involve smaller, and more focused clinical trials than would occur if the drug were studied in a broader group of patients with a wide range of clinical manifestations. The use of biologically and clinically meaningful surrogates as non-mortality endpoints should be allowed. The labeling of drugs approved using this pathway would make clear that the drug is narrowly indicated for use in limited, well-defined subpopulations in which the drug's benefits have been shown to outweigh its risks." Allowance of such designs and endpoints should obligate Sponsors to conduct evaluations of longer-term, post-approval safety and outcomes.

Quintiles' research suggests that patients are willing to use therapies developed under an accelerated pathway. This is based in part on a 2012 survey of patients living with chronic disease, which found that patients want access to new medicines sooner, and that those in greatest need are willing to accept

[4] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp&mid=WC0b01ac05807d58ce

[5] https://www.federalregister.gov/articles/2013/01/15/2013-00607/creating-an-alternative-approval-pathway-for-certain-drugs-intended-to-address-unmet-medical-need

more uncertainty about a new therapy if it offers potential to improve their health:[6] 71% of U.S. patients surveyed agreed that: "*We take too long to make drugs available, which costs lives by forcing people to go without potential beneficial therapies.*

Quintiles maintains not only that such a pathway is an important way to bring new therapies to patients in need, but also that it is a feasible pathway that can be operationalized today.

Recommended Approach

FDA should adopt, on a pilot basis for conditions meeting agreed criteria, an alternative development pathway where new entities meeting safety and efficacy endpoints (including clinically and biologically meaningful, non-mortality surrogates) in smaller, well-defined populations are granted limited market approval for that specific sub-population. The sponsor would then conduct additional studies on expanded populations to evaluate safety and potential expansion of label to broader population, while monitoring real-world outcomes in treated patients.

Today's technologies and science provide the ability to keep patients safe while accelerating access in ways not envisioned with the original Gold Standard three-phase randomized clinical trial (RCT) model. Below are five key capabilities to operationalize this approach. Each would improve drug development today. Together they would allow for the more aggressive step of allowing an Alternative Development Pathway. They would create a rigorous, confidence-inspiring pathway based on pre-registration studies in narrowly defined subpopulations, together with post-marketing registries and observational studies to ensure safe use:

[6] Quintiles. The New Health 2012 Report: Rethinking the Risk Equation in Biopharmaceutical Medicine. Available at: http://newhealthreport.quintiles.com/wp-content/themes/new_health_report/media/pdf/Quintiles_NewHealthReport_2012.pdf

a) **Data Analytics to Power Accurate Studies**: The first key to making this work is being able to incorporate real-world data to inform trials. Quintiles and others have this capability and use it today. Congress should: 1) direct FDA to encourage its use; and 2) drive availability of de-identified data. This would enable better planning and design of pre-registration trials in stratified subpopulations so that these studies have the maximum likelihood of providing clinically and statistically significant findings. Advanced trial design tools are available now to incorporate real-world data into trial designs. For example, we use a tool called Quintiles Infosario™ Design that allows us to query real-world data including de-identified electronic medical records (EMRs) representing more than eight million patient lives. With this capability, questions such as "What are the anticipated event rates for specific sub-populations?" and "What sites are likely to see the specific populations eligible for this treatment?" can be answered. Those insights then can be used to perform simulations of possible trial designs in real time to yield more informative and efficient studies.

b) **Precise identification of the patient subpopulation**. Recent advances allow for the use of genomics, RNA sequencing, expression analysis, soluble and tissue-based biomarkers, and statistical methodologies to identify appropriate subpopulations. With these technologies, the patients who are most likely to benefit can be identified, optimizing the benefit-risk profile. However, we need FDA's continued acceptance and support of stratifying biomarkers as valid inclusion criteria and Congressional support of collaborative efforts to combine and study existing genomic data, and to encourage ongoing banking of samples.

c) **Higher-quality study sites to limit variability**. Smaller studies in stratified subpopulations intensify the need for research precision exceeding currently accepted levels. In order to limit variability, the accelerated pathway will require higher-quality study sites than are currently required for traditional studies. This could undermine the validity of smaller stratified trials. Collaborations with investigators and the use of sites that exceed existing quality and operational metrics will be necessary. Specialized sites are increasingly being used in clinical research. Others commenting to the Committee have called for the creation of Clinical Trial Networks that meet agreed upon standards. Quintiles supports this concept, yet suggests that Congress consider existing networks and standards established through current private sector initiatives. For example, Quintiles has a Prime and Partner Sites program that identifies and partners with sites and investigators who are capable of delivering these enhanced research capabilities, and monitors their performance with metrics and ongoing review.

d) **Real-world drug use in approved subpopulations**. Registries can be used to evaluate the efficacy and safety of a new therapy in the narrowly defined subpopulation in routine clinical practice for which safety and efficacy have been demonstrated in pre-registration studies. Observational studies can be used to assess real-world efficacy of the drug in all patient populations, even those not specifically evaluated in pre-registration studies. In our experience, the combination of well-constructed registries and scientifically rigorous observational studies augments insights gained from prospective pre-registration studies. It also provides knowledge about the benefit-risk profile of a drug in the real-world setting most relevant to practicing healthcare providers and patients.

e) **Monitor use of medicines in patients not participating in registries** to identify and evaluate off-label use. Prospective observational studies based on EMRs could be conducted to monitor medicine use in patients who are not enrolled in registries or observational studies. This would provide insight into the real-world use of the therapy and help to assess the percentage of prescriptions that are consistent with the labeled indication, the ways in which patients who utilize a drug off-label differ from the population for which the drug was approved, and the outcomes in such patients.

All the necessary pieces are in place to embrace alternative pathways for drug evaluation and approval. The tools and data required to identify and monitor patients correctly exist now. An integrated approach to the continuum of development and prescribing can be identified. To borrow from the technology world, we must "think big, start small, and scale fast" to make this alternative pathway a reality so that patients in need can benefit without delay. Congress should clarify, and if necessary amend, FDA statutes to allow and encourage the agency to adopt new pathways for development of new medicines, biologics and devices (rather than defaulting to an up or down vote on 'safe and effective').

Harmonizing Regulatory Requirements Internationally: Today's drug development is a global endeavor. What determines where drugs are tested and made available is often complicated and made more expensive by varying requirements for studies across geographies, including between the U.S. and EU. For instance, preparing different regulatory authorization applications for each country, for the same studies, requires enormous staff time and thus cost, with little benefit or meaningful differences. At times, different requirements for studies can even lead to the discontinuation or significant delays in advancing of promising development programs due to the prohibitive cost of doing large-scale studies differently for different authorities.

Quintiles has particular experience of the need for harmonization, having seen introduction of a promising program for a rare disease slowed by several years because one region required a trial with a placebo arm, the other (where a competitor product was marketed) required a trial including standard of care. Given the limited population for this investigational therapy, there were not enough patients to carry out both a placebo controlled and a non-placebo controlled study in a timely manner. This resulted in significant delay in making the drug available to patients and unnecessary cost of running separate studies.

Increased harmonization would reduce redundancies that have significant time and cost implications, and improve availability of medicines for patients who need them.

Recommended Approach: There has been a gradual move towards more harmonization through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); this could be expanded and accelerated. The U.S. should increase cooperation and harmonization with other countries, starting with the EU, and consider mutual recognition of new drug regulatory authorization applications in the U.S. and EU. Congress should consider adding a goal to PDUFA 6, setting milestones for increased harmonization.

On behalf of Quintiles, thank you again for the opportunity to be part of today's discussion on modernizing clinical trials. I will be more than happy to expand upon any of the recommendations we have offered today, and look forward to your questions and participating further in the 21st Century Cures Conversation.

Mr. PITTS. Chair thanks the gentlelady.

And thanks all the witnesses for very thoughtful testimony. And we will begin questions and answers.

At this point, let me ask you for a unanimous consent request to submit for today's hearing record four items: Letters to the editor of the New England Journal of Medicine questioning a number of assertions made in an article Dr. Kesselheim and others had published in the same publication on March 27. And these letters include a letter from Mark McClellan of the Brookings Institution and Ellen Sigal of the Friends of Cancer Research, a letter from the Infectious Diseases Society of America, and a letter from the Leukemia and Lymphoma Society.

Without objection, so ordered.

[The information follows:]

The contribution of tumoral D3 to sunitinib-associated hypothyroidism probably varies from one tumor type to another. The findings of Foukakis et al. show that D3 induction by sunitinib extends beyond GISTs to breast cancer, and the absence of D3 induction that we observed in isolated breast-cancer cells suggests that sunitinib may indirectly stimulate tumoral D3 in vivo. Although we agree that the role of tumoral D3 in the absence of therapy should be further investigated, the ability of tumoral D3 to cause hypothyroidism without treatment with tyrosine kinase inhibitors is well established in hemangiomas and other tumors.[4] With regard to GISTs, the index patient we described had extremely high D3 expression in tumor tissue obtained from his original surgery (before any medical treatment), and the unusually high prevalence of hypothyroidism among adults with GISTs before sunitinib treatment (22%)[5] suggests that consumptive hypothyroidism occurs in untreated patients. For this reason, vigilance is justified in this population, and we recommend that thyroid function be assessed in any patient with a large GIST burden, even if tyrosine kinase inhibitors have never been used.

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Since publication of their article, the authors report no further potential conflict of interest.

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New FDA Breakthrough-Drug Category — Implications for Patients

TO THE EDITOR: Darrow et al. (March 27 issue)[1] present an incomplete and misleading review of the Food and Drug Administration (FDA) programs that are available to expedite drug development, review, and approval. As the authors note, drug regulation involves balancing the potential benefits of access to a therapy against the potential risks associated with the drugs and the prognoses of patients with the diseases that the therapies are intended to treat, on the basis of evidence of safety and effectiveness. Any evaluation of drug regulation should present a complete picture of the available evidence regarding the effect of reforms, including their impact on facilitating the generation and effective use of evidence.

The FDA has four distinct mechanisms to speed the development and availability of drugs for treating serious or life-threatening conditions: priority review, accelerated approval, fast-track review, and most recently, breakthrough therapy.[2] Although these approaches all aim to advance the availability of safe and effective products, they use different selection criteria and target different parts of the drug-development process.

Darrow et al. claim that the FDA applies expedited-approval programs too liberally, noting that 56% of drugs approved in 2012 used expedited-approval pathways. However, the authors offer no analysis of these drugs and do not acknowledge that almost half the new drugs that were approved in 2012 were for orphan diseases or cancers, many of which had no effective treatment option.

Most drugs that have received accelerated approval have completed rigorous postmarketing studies, been converted to full approval, and often become standard of care. Furthermore, the FDA has taken notable steps, including its Sentinel Initiative, to enhance the availability of postmarketing safety evidence that is very difficult to obtain in the premarket setting.[3]

Nothing in law or FDA guidance indicates that the breakthrough-therapy designation lowers the standards for approval, nor do the au-

thors provide evidence to support this claim. The breakthrough-therapy designation was created to facilitate a collaborative "all hands on deck" approach between the FDA and the drug sponsor on the basis of preliminary clinical evidence of substantial improvement over existing therapies for a serious or life-threatening disease.[4] This approach does not confer a less rigorous path to approval. The majority of the drugs receiving the designation are still undergoing clinical trials, and only four have received FDA approval. All four are clear advances in the treatment of life-threatening diseases that previously lacked effective therapies. FDA programs have evolved over recent years to support the development and review of products that have had a lasting effect on disease treatment in the United States, positively affecting thousands of lives.

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Dr. McClellan reports receiving payment to serve on the board of directors of Johnson & Johnson. No other potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1405337

TO THE EDITOR: The Infectious Diseases Society of America (IDSA) is concerned that the article by Darrow et al. misrepresents new legislation that would allow the FDA to approve antibiotic agents on the basis of small clinical trials in limited populations — specifically, in patients with serious or life-threatening infections and no other treatment options. New antibiotics that are approved through this pathway must be shown to be safe and effective and would carry a special label telling clinicians to use them with extreme care and only for patients with unmet needs. The bill also directs the FDA to review marketing materials in advance and directs the Centers for Disease Control and Prevention to monitor the use of these drugs.

As an infectious diseases physician, I share the authors' concern about approving potentially risky drugs. But that concern must be balanced with the reality that patients are dying because we lack effective antibiotics to treat the infecting organisms. For years, the IDSA has been fearful of a return to a preantibiotic era. Sadly, for more and more patients, that fear is today's reality because the antibiotic pipeline is nearly dry.

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Dr. Murray reports serving as the president of the Infectious Diseases Society of America; receiving consulting fees from Rib-X Pharmaceuticals, Durata Therapeutics, the Medicines Company, Achaogen, GlaxoSmithKline, Theravance, and the Innovative Medicines Initiative Joint Undertaking (European Union grants review); receiving lecture fees from Pfizer; and receiving research funding from Johnson & Johnson, Astellas Pharma, Cubist Pharmaceuticals, Forest Pharmaceuticals, and Theravance. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Darrow et al. imply that the ability of severely ill patients to make critical decisions about their therapy is impaired by their dire situations. The Leukemia and Lymphoma Society (LLS) believes that patients, in concert with their physicians, are in the best position to determine what is right for them and how much risk they are willing to take. Such treatment decisions are increasingly personalized, thus making it difficult for broad populations to be treated similarly. Therefore, the LLS is fully supportive of early-access programs, including compassionate-use programs, for patients who are out of other options. Moreover, our patients have benefited from expedited-approval pathways at the FDA, because such approaches accelerate access. We applaud the FDA for approving two breakthrough-therapy medications for hematologic cancers (ibrutinib [Imbruvica, Pharmacyclics and Janssen Biotech]

and obinutuzumab [Gazyva, Genentech]) that are offering promise for patients with limited alternatives. We do agree that regulations requiring pharmaceutical and biotechnology companies to follow through on postmarketing studies to confirm data in a timely fashion should be strictly enforced and that the FDA should continue to ensure compliance with these regulations.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: The article by Darrow et al. summarizes prior government efforts to expedite the availability of new therapeutics and discusses the implications of the breakthrough-therapy designation. It is worth clarifying that gemtuzumab ozogamicin was not approved for the treatment of pediatric leukemia.

Three trials evaluated the efficacy and safety of the single agent gemtuzumab ozogamicin. The population for the initial report included 142 patients with a median age of 61 years who had a first relapse of acute myeloid leukemia (AML).[1] A total of 30% of the patients had remission. The FDA granted approval for gemtuzumab ozogamicin in the treatment of patients with a first relapse of CD33-positive AML who were 60 years of age or older and who were not considered candidates for cytotoxic chemotherapy.[2,3]

However, the required postapproval study, combining gemtuzumab ozogamicin with daunorubicin and cytarabine in adults under the age of 61 years with new-onset AML, did not confirm clinical benefit.[4] This confirmatory study was performed in a clinical setting that differed from the setting of the original studies.[2] The sponsor voluntarily withdrew the new drug application in 2010.

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Dr. Ricart reports owning stock in Pfizer. No other potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: McClellan and Sigal overlook the fact that the FDA itself acknowledges that its innovations expediting drug approval lower the required evidentiary threshold. The agency describes the fast-track designation as a result of patients' willingness to accept "greater risks" from products treating life-threatening illnesses[1] and has noted that accelerated approval may expose patients to "drug[s] that will ultimately not be shown to provide an actual clinical benefit."[2]

The new breakthrough-therapy designation may not lower evidentiary standards in the same manner as other expedited-approval programs, but it can do so indirectly by generating premature enthusiasm that increases pressure to approve and prescribe a drug. This approach can lead to uncontrolled or truncated trial designs that are less robust than standard trials, and it can normalize the regulatory use of biomarkers that are less likely to predict clinical outcome.[2] These expedited-approval programs have indeed altered approval standards: although the legal standards of "safe" and "effective" remain, the evidentiary standards for meeting those criteria have been loosened. Although the FDA Sentinel Initiative can provide some postmarketing information, the agency is still learning how to use this tool,[3] and postmarketing surveillance should not replace adequate premarket assessment.

Although Murray's warning of a return to a preantibiotic era is a call to action, so too is the possibility of regressing to the pre-1962 era during which ineffective drugs often received FDA approval. This concern is particularly salient for

new antibiotics, which are usually approved on the basis of trials showing noninferiority (rather than superiority) to comparator agents. These agents are also withdrawn from the market more commonly than all other drug categories.[4] Early access can benefit patients, as Velleca asserts, but only if the drug is in fact effective — the very question that only rigorous evidence development can answer. His contention that patients and physicians "are in the best position to determine . . . how much risk they are willing to take" may be true but minimizes the crucial role of governmental benefit–risk assessment of medications. Pressing treatment needs should be met with intensified development efforts, not new designations.

Ricart clarifies the original indication of gemtuzumab ozogamicin, which is now reflected in the online version of our article.

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Since publication of their article, the authors report no further potential conflict of interest.

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Procedural Sedation and Analgesia in Children

TO THE EDITOR: The video by Krauss et al. on procedural sedation and analgesia in children (April 10 issue)[1] was thorough and detailed. However, I am very concerned that 45 seconds into the video an injection into intravenous tubing pushes air bubbles toward the patient. The potentially disastrous consequences of air in intravenous lines are well known, particularly in children with intracardiac shunts.

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TO THE EDITOR: Pediatric patients have limited respiratory reserve and are susceptible to the rapid development of hypoxemia. The emergency equipment mentioned by Krauss et al. does not address the management of an unanticipated difficult or impossible bag-mask–ventilation scenario or the use of emergency airway devices, including a laryngeal mask airway of the appropriate size,[1] an endotracheal tube, and a laryngoscope, which should also be available. Furthermore, the authors state that the administration of supplemental oxygen before and during sedation renders pulse oximetry ineffective with regard to early warnings of respiratory depression and recommend the use of capnography when supplemental oxygen is used. These aspects of the video could lead to the misconception that the observation of ineffective pulse oximetry in the early detection of hypoventilation is related to the administration of supplemental oxygen or that capnography cannot be used if supplemental oxygen is not used simultaneously. Nevertheless, supplemental oxygen is recommended before and during sedation, especially in pediatric patients, owing to their greater susceptibility to hypoxemia.

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Mr. PITTS. I will now begin the questioning and recognize myself, 5 minutes for that purpose. And I will start with you, Dr. Siegel.

Despite advances in science and technology, the duration, cost, and failure rates of clinical trial costs have grown exponentially, leading to delayed access and higher costs for patients. How can we reverse these trends?

Mr. SIEGEL. Well, I think there is a number of topics that have been touched on today that could help address the issues around duration and cost and failure of clinical trials. Those would include the establishment of networks that can allow one to plug in, either through trials such as Lung-MAP or through a series of trials, new therapies, and to relatively standardized approaches, with standardized startups and experienced investigators and standardized protocols. The better use of biomarkers and integrating them into trials, genomic and proteomic information to identify patient groups at risk, to identify early responders and the use of those sorts of data to adapt trials while in conduct also offer the opportunity to reach either success or failure faster with a product, and thereby to reduce the cost of product development.

Mr. PITTS. How can we improve the process by which FDA qualifies novel drug development and review tools such as biomarkers and patient-reported outcome measures, and what would this mean for modernizing clinical trial designs?

Mr. SIEGEL. Is that directed to me?

Mr. PITTS. Yes, Dr. Siegel.

Mr. SIEGEL. It should be clear, first of all, that any sponsor or company or investigator can propose for any trial the use of a patient-reported outcome or a biomarker regardless of whether or not a patient, the FDA has qualified it. The qualification process allows a broader use and acceptability and is intended for use when many groups want to come together and bring together the data that demonstrate the utility of a biomarker or a tool for a particular purpose. It does appear that that process has been relatively scantily used. I think with the creation of more consortia and networks focused on diseases, there is an opportunity to use it more. I do not have expertise in how the process might be improved.

Mr. PITTS. OK. Mr. Murray. What part of the clinical research process consumes the most time for medical devices, and what are the major reasons device trials are moving overseas?

Mr. MURRAY. There are a couple reasons. As I mentioned during my testimony, early feasibility studies in getting to the point of actually having the device ready to start a pivotal study takes on average 6 ½ years and $36 million. That is because there needs to be assessments done during the early phase. Medical devices are physical constructs and oftentimes can only be evaluated effectively in humans. So those early feasibility studies are extremely important. So streamlining that early feasibility process, IRB reviews, legal reviews for innovative new technologies can take very long, and having a process that is more consistent and more predictable in an environment where each site has unique and different requirements will help reduce the delays.

Additionally in today's environment we have the situation where a lot of scientifically valid data is already available outside the

U.S., and the opportunity to incorporate that data and use it for informed decisions in the U.S. could radically reduce the cost.

Mr. PITTS. To pursue that a little bit, given the current reality, what can Congress do to help FDA accept the data collected outside the U.S. to ensure American patients are getting access to the American innovations sooner?

Mr. MURRAY. One of the opportunities is to look at rebalancing the pre- and postmarket requirements. If you look at reducing slightly the confidence interval in the premarket perspective, for example, if the confidence interval in a trial were modestly reduced from 95 percent, say, to 90 percent in the premarket phase, that could radically reduce by as much as half the size of the clinical trials required; and as long as there is appropriate controls and mechanisms in place to continue to monitor those patients post market, that would encourage more products to be approved and could reduce the time to market.

Mr. PITTS. Ms. Stafford, how can real world data enable us to learn more about the benefits and risks of a product, both in the clinical trial setting and once a product goes to market, and how can electronic health records and increased data sharing play a role in this regard?

Ms. STAFFORD. One way that it can help in terms of using the EHR is actually in the feasibility of a trial and using the data that we have in the real world to help us design the best trial possible and using that data up front to even help us identify and find the right patients for the trials based on prior experience with similar drugs or like therapeutic areas. And real world is our ability to, it really goes into the master protocol or the adapted design and really bringing in data sooner and helping to make these decisions sooner based on the real-world information that we have.

Mr. PITTS. My time is expired. The Chair recognizes the ranking member, Mr. Pallone, for 5 minutes of questions.

Mr. PALLONE. Thank you, Mr. Chairman. I would ask unanimous consent to enter into the record an article from the New England Journal of Medicine by Drs. Darrow, Avorn, and Kesselheim, and also a statement by Ms. DeGette.

Mr. PITTS. Without objection, so ordered.

[The article and the prepared statement of Ms. DeGette follow:]

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Mary Beth Hamel, M.D., M.P.H., *Editor*

New FDA Breakthrough-Drug Category — Implications for Patients

Jonathan J. Darrow, S.J.D., J.D., M.B.A., Jerry Avorn, M.D., and Aaron S. Kesselheim, M.D., J.D., M.P.H.

U.S. pharmaceutical regulations are based on the principle that patients should not be exposed to new prescription drugs until their efficacy and safety have been shown. Since 1962, the Food and Drug Administration (FDA) and Congress have balanced the efficient review of investigational drugs with the need to withhold judgment until sufficient evidence is available to clarify the benefit–risk relationship. Misjudging these competing interests in either direction causes important problems. On the one hand, the evidentiary hurdles of the FDA are often criticized by pharmaceutical companies and patient advocacy groups for slowing access to promising therapies. On the other hand, truncated premarket review can lead to the approval of drugs that are ineffective, unsafe, or both.

These dangers were once again made clear in October 2013 when approval was briefly suspended for ponatinib, a medication to treat leukemia that had been approved just the year before on an accelerated basis. Emerging data showed that 24% of the patients who had been followed for a median of 1.3 years and 48% of those who had been followed for a median of 2.7 years had serious thromboembolic events, including myocardial infarction and stroke.[1] The drug was allowed back on the market in December 2013 with more limited indications and a restricted distribution system.

The latest development in the FDA approach to ensuring the safety and effectiveness of marketed prescription drugs occurred in July 2012, when Congress created a new category of "breakthrough therapy" in the FDA Safety and Innovation Act (FDASIA). A breakthrough therapy was defined as a new product to treat a serious disease for which preliminary clinical evidence suggested substantial superiority over existing options on one or more clinically significant end points.[2] Lawmakers intended the designation to speed to market a limited number of products that showed "exceptional results for patients."[3] Lauded by policymakers,[4] consumer advocates,[5,6] and the FDA itself,[7] the breakthrough-drug pathway has been embraced by industry[8] and has produced early results far exceeding predictions. From October 2012 through September 2013, the FDA received 92 applications for the breakthrough-therapy designation, of which 27 were approved and 41 denied (24 applications were still pending).[9] Although some of these agents may end up being truly transformative for patient care, the breakthrough-therapy designation also raises the possibility of a surge in new drugs that have been approved on the basis of limited clinical data.

There is ongoing controversy over the FDA standards for the approval of investigational drugs. In this article, we briefly summarize prior government efforts to expedite the availability of new therapeutics, and we discuss the clinical, ethical, and regulatory implications of the breakthrough-therapy designation.

HISTORY OF EARLY-ACCESS AND EXPEDITED-APPROVAL PROGRAMS

The Food, Drug, and Cosmetic Act (FDCA) of 1938 prohibited the routine therapeutic use of investigational drugs, although in practice physicians easily obtained such drugs outside of clinical trials.[10] A sea change came when the 1962 Kefauver–Harris Amendments to the FDCA required affirmative FDA approval on the basis of trials in humans before new drugs could be marketed. Regulations in 1963 divided these trials into three phases — small, phase 1 safety trials; intermediate-size, phase 2 efficacy studies; and large, controlled, phase 3 studies — forming the basis for a new drug application (NDA).

There was concern that extended study before approval could prevent timely patient access to potentially lifesaving medicines. The FDA first

responded by adopting pathways to allow treatment use before approval. In the 1960s, early-access programs (also called compassionate-use programs) allowed limited patient access to investigational drugs, although these programs had no written rules and were flexibly applied. The demand for experimental cancer drugs was particularly strong, leading the FDA to publish in 1979 its first official early-access policy for such drugs.

Pressure from physicians and patients intensified with the AIDS crisis of the 1980s, a pivotal episode in the evolution of the FDA drug-approval policies. Demonstrations by AIDS activists at FDA headquarters brought widespread attention to the lag times between submission and agency approval of new medications,[11] although the perception that the FDA did not rapidly assess drugs intended for patients with human immunodeficiency virus (HIV) infection may have been exaggerated.[12] In 1987, regulations for treatment investigational new drug applications (treatment INDs) formalized the procedures for obtaining early access to investigational drugs outside of clinical trials.[13] Three years later, the FDA proposed making unapproved drugs for HIV/AIDS available even sooner by means of a parallel-track mechanism[14] for patients with HIV/AIDS who were unable to enroll in clinical trials.

In the 1980s, early-access options were joined by FDA initiatives to hasten drug approval. In 1988, the FDA created a fast-track component (Subpart E) of its rules to "expedite the development, evaluation, and marketing of new therapies"[15] for serious and life-threatening conditions by, for example, eliminating phase 3 trials. The provisions were modeled on the testing and approval of the HIV drug zidovudine, which occurred over a period of only 2 years and included a single, well-designed phase 2 trial. In 1992, the FDA initiated an accelerated-approval pathway (Subpart H) to allow approval on the basis of surrogate end points that were seen as reasonably likely to predict patient benefit.[16] Subpart H shortened the clinical-investigation process by permitting trials to end before the occurrence of hard clinical end points (e.g., hospitalization, myocardial infarction, and death).

The same year that the FDA finalized Subpart H, Congress enacted the Prescription Drug User Fee Act (PDUFA), which authorized the FDA to collect "user fees" from pharmaceutical manufacturers. Although increased Congressional appropriations to the FDA had already reduced NDA review times by the late 1980s,[17] PDUFA allowed the FDA to hire more scientists and further expedite the review of drug applications.[18] PDUFA also set formal deadlines of 6 months for priority applications and 12 months for standard applications (shortened to 10 months in 2002). Within 1 year after the enactment of PDUFA, the FDA had acted on 93% of NDAs within the new deadlines.[19] The user fees were restricted to the approval of products; it was not until 2007 that the FDA had the authority to allocate them to postapproval drug-safety activities.[20] Under FDASIA, the FDA review deadlines now begin to run 60 days after NDA submission.[21]

BENEFITS AND RISKS OF EXPANDED ACCESS AND EARLY APPROVAL

The FDA has estimated that more than 100,000 patients have received investigational drugs for serious or life-threatening conditions through the use of treatment INDs.[22] For investigational drugs that ultimately prove to be superior to existing options, these early-access programs benefit patients by allowing new therapies to reach them sooner. In addition, expedited development and approval programs have shortened the clinical development period, allowing earlier access for the broader patient population. Subpart E, for example, reduced the average clinical development time from 8.9 to 6.2 years, whereas drugs benefiting from accelerated approval averaged just 4.2 years.[23] NDA review times have also decreased dramatically, from more than 30 months in the 1980s to 14.5 months by 1997[24] and to 9.9 months for applications received in 2011.[25]

The immediate result of PDUFA was a spike in approvals during the mid-1990s as backlogged applications were processed,[26] but the number of approvals each year soon returned to historical averages.[27] Although the FDA was once considered by some to approve drugs too slowly,[28] drug approvals since 2000 have been quicker in the United States than in Canada or Europe. From 2001 through 2010, the FDA approved 64% of novel therapeutic agents earlier than the European Medicines Agency.[29]

However, early access and shortened development and review times have also been associated with negative public health outcomes. Drugs approved shortly before the PDUFA-imposed deadlines have been found to be more likely to

have postmarketing safety problems — including safety withdrawals and added black-box warnings — than were drugs approved at any other time.[30,31] Other investigators have reported that drugs receiving faster reviews have more spontaneous reports of drug-related adverse events, although these data are controversial.[32-35] Among drugs first approved abroad, those with more foreign-market experience before U.S. approval are less often associated with serious adverse drug reactions.[35,36]

Such findings are predictable because of the more limited data on which expedited drug approvals are based. Although neither the fast-track nor the accelerated-approval pathways changed the legal standard for approval — which is still effectiveness with acceptable risk — they reduced the quantity of evidence needed to meet this standard and altered the nature of that evidence. For example, cancer drugs approved during the previous decade on the basis of limited clinical trials — nonrandomized, unblinded, single-group, phase 1 and phase 2 trials that used intermediate end points rather than patient survival — had a 72% greater odds of serious adverse events occurring in their pivotal trials than did cancer drugs that were approved with more-rigorous studies.[37] A recent study showed that drugs benefiting from expedited approval programs were tested for efficacy in a median of only 104 patients, as compared with 580 patients for nonexpedited review.[38] Data collected with the use of early-stage clinical-trial methods are unstable and may be subsequently disproved in larger, more-rigorous trials.

Concerns about potentially inaccurate assessments of the benefit–risk ratios led the FDA, beginning in approximately 1970, to condition some approvals on the conduct of postapproval (phase 4) confirmatory studies. The proportion of new drugs that were subject to these postapproval obligations increased from approximately 30% in the early 1980s to approximately 80% in the early 2000s.[39] Unfortunately, the performance of these follow-up studies has often been markedly delayed[40] or not initiated at all.[41] Gemtuzumab ozogamicin was approved in 2000 for the treatment of a rare type of leukemia on the basis of limited data, but it was withdrawn from the market in 2010 after confirmatory trials initiated in 2004 showed increased mortality and no efficacy.[42]

Concern over the timely conduct of postapproval studies led Congress to strengthen the enforcement authority of the FDA in the FDA Amendments Act of 2007. However, as recently as 2011, postmarketing-study commitments for more than 40% of drugs had not yet been started, whereas the number with delays had doubled since 2007 to approximately 13%.[38,43] Completion times also appear to range widely: a report from the Office of Oncology Drug Products regarding a sample of oncology drugs approved by way of the accelerated-approval pathway showed that it took 0.8 to 12.6 years before postmarketing trials were completed (median, 3.9 years).[44] Bedaquiline, a medication for the treatment of multidrug-resistant (MDR) tuberculosis, was approved in 2012 on the basis of the surrogate end point of sputum-culture conversion, even though the pivotal studies also showed an incidence of death (generally from tuberculosis) that was five times as high among patients given the drug than among those randomly assigned to receive standard treatment for MDR tuberculosis. The impact on individual patients must be further studied since there is a need for additional treatment options for this highly contagious disease. The confirmatory randomized trial that was mandated for bedaquiline was not required by the FDA to be completed until 2022.[45]

BREAKTHROUGH THERAPY — RATIONALE AND POTENTIAL OUTCOMES

In approving FDASIA, Congress anticipated that the use of modern evaluation tools earlier in the drug-development cycle could result in "fewer, smaller, or shorter clinical trials." During Congressional hearings in 2012, advocacy and industry organizations supported the creation of the new breakthrough-therapy designation to abbreviate or combine traditional clinical phases to enhance earlier patient access.[46,47] Support for the law also came from officials within the FDA Center for Drug Evaluation and Research who, in November 2013, praised the "much larger treatment effect" achieved by some recent "molecularly targeted therapies" that aim to benefit subgroups of patients with "cancer, genetic diseases, and . . . other serious illnesses."[7] The article defended the new expedited-development program, suggesting that "when a large effect in a serious disease is observed early in drug development, it seems excessive to conduct a prolonged clinical development program that encompasses

traditional trial phases."[7] According to this view, the new designation could make possible streamlined clinical development that would lead to more rapid approval.

The breakthrough-therapy designation is the latest addition to the expanded-access and expedited-approval programs of the FDA (Table 1). In recent years, the exceptions have been more common than the rule; among the 39 new drugs approved in 2012, a total of 22 (56%) were approved by means of at least one of the accelerated-approval, fast-track, and priority review programs, and 9 of these (23% of the total) qualified for more than one program.

Regulatory efficiency was identified as a major outcome of the breakthrough-therapy designation,[8] but the benefits offered in FDASIA are already largely available through existing legislation, regulations, or standard FDA practice. For example, FDASIA commits the FDA to working closely with sponsors of breakthrough therapies.[7] However, Subpart E (1988) offered "early consultation between FDA and drug sponsors," emphasized the importance of meeting with the FDA to ensure efficient phase 2 trial design, and specified that senior FDA officials would actively facilitate the conduct and evaluation of clinical trials.[56] FDASIA notes that breakthrough therapies may also benefit from the assignment of a "cross-disciplinary project lead" to facilitate efficient review, but it is unclear how this will improve on existing coordination of staff efforts.

The breakthrough-therapy designation continued the trend of applying increasingly flexible evidentiary standards to determine the qualification for expedited development and approval programs. Certain drugs have long been approved on the basis of well-established surrogate end points.[51] The accelerated-approval pathway (1992) began to allow approval on the basis of "less than well-established surrogate endpoint[s]."[51] By contrast, one way to qualify for the new breakthrough-therapy designation (2012) is by showing "an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint, but strongly suggests the potential for a clinically meaningful effect on the underlying disease."[55] This more flexible standard would apply to a broader range of potential new therapies. The law requires that breakthrough drugs must eventually be approved or rejected under the normal FDA approval standards, but as was seen with the bedaquiline approval for MDR tuberculosis, such confirmation may not be required for years.[45]

Once the breakthrough-therapy status has been granted on the basis of preliminary evidence, it may be difficult to temper demand (whether early access or postapproval) even if the drug is revealed to be less effective or more harmful than initially believed. Decision theory suggests that when a decision is less reversible, more care should be taken in reaching the initial determination.[57] This tension emerged most recently around bevacizumab, which was approved for the treatment of metastatic breast cancer on the basis of surrogate end points under the accelerated-approval pathway. When subsequent studies showed no increase in patient survival, withdrawing the indication took nearly a year and generated substantial opposition.[58] Some insurers still cover off-label use of the drug for this non–evidence-based purpose.

Deferring rigorous study until after a drug is approved can also undermine and delay evaluation of its benefit–risk profile.[38] Once a drug is approved, enrolling patients in clinical trials to determine efficacy is more challenging than before approval, because patients have the choice of receiving the drug in the normal course of therapy or enrolling in a trial in which they may be randomly assigned to usual care. This concern is magnified when deferred study is paired with earlier designations that may be interpreted as official endorsements.

CONCLUSIONS

The 27 breakthrough-therapy designations granted by the FDA in the first 9 months of 2013 are unlikely to represent a sudden and dramatic increase in the pace of pharmaceutical innovation, given that an average of 25 new molecular entities were approved annually during the previous decade. Another interpretation of the rapid popularity of the designation is that it has created the appearance of progress while enhancing the visibility of promising early-stage drugs that may be no more likely than before FDASIA to confer large benefits to patients. The breakthrough-therapy designation is also likely to further increase public pressure on the FDA to approve such products. Few would argue about the need for pathways to bring safe and effective new drugs to market quickly, especially for life-

Table 1. **Early-Access and Expedited-Approval Programs of the Food and Drug Administration (FDA).***

Program	Year Created	Origin	Limited to Serious or Life-Threatening Conditions	Provisions Addressing Efficacy or Evidence of Efficacy
Early access				
Group C	1979†	FDA and National Cancer Institute	Yes, cancer	NA‡
Orphan Drug Act, with open protocols§	1983†	Congress	No	Applies to all drugs treating diseases occurring in fewer than 200,000 persons in the United States, regardless of efficacy
Treatment IND	1987†	FDA, later codified by Congress	Yes	In the case of serious disease: requires sufficient evidence of safety and effectiveness, and may be made available for use during phase 3 or during phase 2 in "appropriate circumstances"; in the case of immediately life-threatening disease: requires that the "available scientific evidence, taken as a whole . . . provide a reasonable basis for concluding that the drug 'may be effective and may be made available 'ordinarily not earlier than Phase 2'"[13]
Parallel track	1992	FDA	Yes, HIV/AIDS	Requires "promising evidence of efficacy based on an assessment of all laboratory and clinical data" as well as "evidence of a lack of satisfactory alternative therapy for defined patient populations"[14]
Expedited approval				
Priority review A, B, and C[48]	1974[49]	FDA	No[50]	A indicates important therapeutic gain, B modest therapeutic gain, and C little or no therapeutic gain
Priority review AA	1987	FDA	Yes, HIV/AIDS	"All [NDAs] for AIDS and HIV-related conditions will be classified as AA . . . regardless of their therapeutic potential"[50]
Fast-track review, under Subpart E[15]	1988	FDA, later codified by Congress	Yes	Allows drug to be approved after phase 2; process allows approval on the basis of "well-established surrogate endpoints"[51]
Priority review¶	1992[52,53]	FDA	No[51]	Priority review means that the drug appears to represent therapeutic advance; standard review means that the drug appears to have therapeutic qualities similar to those of already marketed drugs
Accelerated approval, under Subpart H	1992	FDA, later codified by Congress	Yes	Approval on the basis of surrogate end points is reasonably likely to predict clinical benefit; postmarketing studies are required "to verify and describe . . . clinical benefit"[16]
Priority-review voucher	2007	Congress	No	Approval of a tropical disease–treating drug entitles sponsor to transferable voucher to obtain priority review of any new drug
GAIN section of FDASIA	2012	Congress	Yes[54]	Qualified infectious-disease products are automatically eligible for fast-track designation and priority review
Breakthrough therapy	2012	Congress	Yes	Preliminary clinical evidence indicates that the drug may show substantial improvement over existing therapies; designation on the basis of "an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint"[55]

* FDASIA denotes Food and Drug Administration Safety and Innovation Act, GAIN Generating Antibiotic Incentives Now, HIV human immunodeficiency virus, IND investigational new drug, NA not applicable, and NDA new drug application.
† Ad hoc FDA procedures made preapproval access available on an informal basis before this date.
‡ Group C drugs were authorized under the treatment IND program, and informally before that.
§ "Open protocols" and "compassionate use INDs" were some of the terms used to describe types of informal "treatment uses" before the codification of the treatment IND in 1987.
¶ This process replaced the A, B, and C system for new drugs.

threatening diseases for which current treatment options are inadequate. Efforts to promote early access, expedited development, and early approval have existed for decades. Unfortunately, these efforts generally have not been followed by equally energetic efforts to develop rigorous confirmatory data that could refine the indications for the drug or even change its approval status.

There has also been little discussion of the implications of approving breakthrough drugs on the basis of limited data for patients considering therapeutic options and for their physicians. Expedited approval has been championed by patient advocacy groups who think that FDA requirements that delay access to new products infringe on personal autonomy. Of course, this view is not universal among patients.[59] How will patients make informed choices about breakthrough drugs approved with new clinical-trial techniques rather than with traditional randomized trials?

This question is particularly salient for patients with life-threatening illness. Previous research has uncovered important deficiencies in decision making by patients in such precarious situations. One survey showed that, as compared with healthier patients, severely ill patients had less retention of the information that was discussed in the informed-consent process and less-clear understanding of the risks of therapy.[60] Some have suggested that insurers will act as an effective counterweight in the post-approval marketplace by refusing to cover breakthrough products with clinical activity that is either unconfirmed or does not justify the high cost.[61] In Europe, centralized payers serve as a barrier to the widespread use of available but marginally useful clinical therapies.[62,63] However, in the United States, the greater fragmentation of the insurance market and the greater sense of entitlement to all available treatments make it unlikely that this counterbalance will be as effective.

Even before the first breakthrough drug has been approved, lawmakers have started discussing the next pathway aimed at further reducing evidentiary requirements to speed drugs to market.[64] On December 12, 2013, a bill was introduced in Congress that would allow the approval of new antibiotic and antifungal medicines on the basis of alternative end points and data sets of limited size so long as the labeling prominently stated that the drugs were indicated for use in a limited and specific population of patients.[65] The bill did not restrict the ability to prescribe such drugs off-label. In the next few years, evidence will accumulate to indicate how well the new breakthrough-therapy designation improves the options of patients with serious and intractable diseases and to what extent it facilitates the market entry of treatments that promise more than they can deliver.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Statement of Rep. Diana DeGette – As Prepared for Delivery Energy and Commerce Subcommittee on Health Hearing: "21st Century Cures: Modernizing Clinical Trials" July 9, 2014

Mr. Chairman, I want to thank you for holding this hearing today.

Through the previous hearings and roundtables we have held on various topics within the 21st Century Cures initiative, we have already learned a tremendous amount about what role Congress should play in helping to further advance and accelerate treatment and cures.

The hearing today will focus on a very important area which has the potential to help millions of patients facing chronic and often incurable conditions – modernizing clinical trials.

The Food and Drug Administration (FDA) has taken great steps in this area – particularly with more flexible approaches to drug and device development. And, the agency is continuing to work on using existing authorities to adapt to advancing technology and new discoveries.

However, there may be areas in which Congress could provide more clarity for FDA, as well as address some challenges that have persisted within the clinic trials settings.

For example, I have introduced legislation in the past that would, among other things, address the lack of consistency across agencies as it relates to human subject research. Currently, there is much confusion for researchers and institutions that receive support from more than one agency due to multiple, and sometimes conflicting, regulations.

As we will hear from our witnesses, there are other areas in which we could help modernize clinic trials without compromising the high safety and efficacy standards we should continue to hold ourselves to.

I look forward to the testimony today and to learning more about this important topic.

Thank you.

Mr. PALLONE. Thank you. I wanted to start with Dr. Kesselheim. Some of you have cited the need to use novel or alternative trial designs as a way to modernize the way clinical trials are conducted, and I want to learn more about one of these in particular, the use of surrogate end points. We have heard a lot about this recently, most notably with the situation surrounding two drugs, Avandia and Avastin, and these drugs were allowed on the market based on a surrogate end point through FDA's accelerated approval pathway.

So I would like to ask you, Dr. Kesselheim, to explain to us a bit more about what surrogate end points are because I am not sure I totally understand what they are and how they are used in accelerated approvals. Specifically, what are the benefits of using surrogate end points? What are the drawbacks or concerns, and how has FDA relied upon surrogate end points appropriately, or have they relied on surrogate end points appropriately in your view?

Mr. KESSELHEIM. Well, a surrogate end point is when we are testing a new drug or a patient wants to take a new drug or get a medical device, they are most interested in extending their lives or improving their symptoms or other kinds of real clinical end points. A surrogate end point is an end point that is not one of those end points but might predict that end point ultimately. So in the case of a diabetes drug, instead of a drug showing that it improves life span or reduces cardiovascular events, it might change the hemoglobin A1C value, which is a biomarker and a surrogate end point that may predict ultimately down the line what happens. The goal of using surrogate end points is to try to shorten the span of clinical trials that are necessary to test a new product.

The problem is when a surrogate end point isn't connected to the final clinical end point and then doesn't predict the final outcome of the drug, and if a drug is approved on the basis of a surrogate end point, then patients may experience bad outcomes even though their A1C is slightly improved or in the case of the tuberculosis drug, even though their sputum is slightly cleared, more cleared of tuberculosis.

So surrogate end points, in order to be used as a basis for new drug approval, need to be validated by being linked clinically, and that is a very difficult and long process and can vary depending on the particular surrogate end point. You know, just take statins, which is a cholesterol-lowering drug, and most people understand, most people agree now that lowering your LDL cholesterol is a surrogate end point towards ultimately lowering your cardiovascular risk. Unfortunately there are some cholesterol-lowering drugs like statins that do a good job of that and then are connected to with surrogate end point does predict clinical outcomes. There are other cholesterol-lowering drugs like Ezetimibe which lowers your LDL but then is not necessarily connected to improved health. And then there are other cholesterol drugs like Torcetrapib, which is a drug that raised your HDL level that again which was thought to act as a valid surrogate but then ultimately did not end up demonstrating actual clinical effects.

Mr. PALLONE. But what about whether you think that the FDA has relied upon these appropriately?

Mr. KESSELHEIM. So I think that the FDA has a very difficult job and relies on surrogate end points in certain limited circumstances where either, A, the surrogate end point has been validated or B, there is a great unmet clinical need. And that was as in the case that you mentioned, the Avastin for metastatic breast cancer case, where everybody believes we need more therapies for metastatic breast cancer, and this appeared to be a good surrogate.

Unfortunately it later turned out that it wasn't, and it increased mortality of patients with breast cancer. And the problem was at that stage it was very difficult for the FDA to then withdraw the indication and now to try to change clinical practice away from using the product because the surrogate end point had sort of caught on.

Mr. PALLONE. It is difficult for the FDA to know when they are valuable or not, in other words?

Mr. KESSELHEIM. Right.

Mr. PALLONE. Let me just ask one more. I am running out of time. Dr. Meyer, you noted that you would caution against shifting confirmatory efforts to the postapproval setting. Can you just expand upon that a little, and what is your view on how FDA has approached the reliance on surrogate end points.

Mr. MEYER. OK. So as far as the proposals to shift the regulatory decision-making more towards the end of phase II relying on real world data for efficacy, I don't think we are at a point with the science where we can rely on that. The kind of evidence we want for assuring effectiveness of a drug at the present time I think can only come through well-conducted, generally randomized trials. I think the fact that half the drugs that fail from phase III to approval fail for efficacy reasons is a good example that even at the end of phase II where there is a lot of promise, that may not be confirmed by randomized control trials.

As far as the FDA's reliance on surrogates, I think on the main, they do a reasonable job on it. I agree that they are in a tough position there, but I think for the most part, they are very judicious about it, and while they may not always get it right, I think the public health balance is such that you would want them to do well most of the time, and I think they do well most of the time.

Mr. PALLONE. Thank you. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman. I now recognize the chairman emeritus of the committee, Mr. Barton, 5 minutes for questions.

Mr. BARTON. Mr. Chairman, I have not been here for the—I listened on TV, but I wasn't here in person, so I am going to pass, but I appreciate your courtesy. I think this is a good panel, and I think the issues they are putting before your subcommittee are excellent, but I appreciate your courtesy.

Mr. PITTS. The Chair thanks the gentleman and now recognizes Dr. Burgess, vice chair of the subcommittee, for 5 minutes.

Mr. BURGESS. Thank you, Mr. Chairman. And again, thanks to our witnesses for being here today.

Mr. Chairman, before I get to questions, I just want to add another unanimous consent request that yesterday's Wall Street Journal, the article by Peter Huber, they did a collection of articles about how things could change in this country to improve things.

In addition to the Tax Code and two-parent families, here was an article by Peter Huber about unleashing molecular medicine dealing with the very issue that we have before the committee today. I would like to put that into the record.

Mr. PITTS. Without objection, so ordered.

[The information follows:]

The Wall Street Journal

Opinion

Ideas for Renewing American Prosperity

If you could propose one change in American policy, society or culture to revive prosperity and self-confidence, what would it be and why?

July 7, 2014 7:53 p.m. ET

Unleash Molecular Medicine

By Peter W. Huber

In the past three decades, drug designers have learned how to craft molecules that modulate specific molecular targets—hence "personalized medicine" that fits precisely targeted drugs to patient-specific molecular profiles. Now, rapidly emerging are literally personal treatments created by reprogramming the genetic code in the patient's own cells.

Scientists have recently developed precise tools for adding, deleting or replacing genes inside live cells—tools that can do in hours or days what took months or years using other gene-editing tools. Reprogrammed stem cells—the progenitor cells that spawn all the rest of our cells—have the unique potential to provide complete cures for a wide range of currently incurable disorders, most notably the thousands of rare but often deadly diseases caused by hereditary genetic factors. Immune-system cells reprogrammed to attack cancers and other diseases have shown enormous promise in early trials.

Unlike conventional drugs, human cell therapies can be synthesized from scratch, one patient at a time, with tools compact and cheap enough to land in hospitals, clinics or laboratories that serve doctors in private practice. The technologies can be used to generate, at relatively low cost, a limitless number of biochemically distinct therapies precisely tailored to the individual patient's needs.

Washington's drug-approval process, grounded as it is in a one-size-fits-all perspective on how drugs are supposed to operate, and anchored in clinical-trial protocols and statistical methods developed decades ago, is lagging far behind the science. We need a regulatory process that can keep pace with a rapid proliferation of highly customized therapies that are grounded in a mechanistic understanding of molecular biology. This will require fundamental changes in clinical-trial protocols and in the type of evidence that is required for drug approval.

Mr. Huber is the author of "The Cure in the Code" (Basic Books, 2013).

Mr. BURGESS. Dr. Herbst, let me ask you a question. You touched on it, but you didn't get much chance, so perhaps you could expound on it a little bit, the use of the laboratory developed tests, I think you put it, the regulating diagnostics for clinical trials?

Mr. HERBST. Right. So this is a big challenge because right now for genetic testing there are 20,000 perhaps tests you know that look at 4,000 conditions. There are many different tests. So how are we going to regulate and develop the right tests to use? In the master protocol we have done is we are using a next generation sequencing platform which is allowing us to look at 250 different genes prior to the trial and then assort those patients to one arm of the trial. So that is an example of where we have designed the test in with a trial; hopefully the whole principle of regulation will then occur, that we will approve the drugs with the test. So that is the hope.

Mr. BURGESS. Now, with the FDA reauthorization that we did 2 years ago, and thank you, Ms. Stafford, for recognizing that achievement. Nobody else paid any attention to the fact that there was a bipartisan, bicameral work done by Congress in an election year that actually worked, so I appreciate the recognition. When we did that, did that allow for the type of flexibility that you are requiring for these laboratory developed tests? Do you think as you use this next generation sequencing, that you will be able to get through the regulatory requirements that you need to?

Mr. HERBST. I believe so. It is a challenge because this is a new paradigm to do a multiplexed series of tests and then use the data from that to put patients on trial, but the benefit we have in this large public-private partnership of the master protocol is we are working very closely with the FDA and with the branch that regulates these diagnostics and getting advice from them. We are working closely with our pharma partners, and we are working closely with the group that we have chosen to do the diagnostic tests, so hopefully we are meeting all the requirements of that should this work and should a drug actually show efficacy, we can then get these tests approved. But I think it is important to look very carefully at what test is being done, the method, the validity, the reproducibility of those tests because there are so many different ways of testing for the same thing.

Mr. BURGESS. Correct. That was actually one of the unanswered questions in FDASIA, so I would appreciate your feedback to this committee. If you find it is working well or not working well, we actually need to hear from you on that, because we never actually came and closed the loop on that and came to a conclusion.

Dr. Siegel, let me ask you a question and your company, and this is a little off topic for you because you were primarily talking about drug approvals, but on the device side, Johnson & Johnson just achieved finally a FDA approval for a device called SEDASYS that assisted in the administration of analgesia and anesthesia for people who are undergoing minor procedures. Minor, by definition, is someone else's procedure, but undergoing procedures that are not open procedures. Can you speak a little bit to the difficulty, because that was a, what, 17-, 18-, 19-year-old regulatory process that this device required, and it seemed pretty simple and straight-

forward. Can you speak to that at all? Are we better now than we were the last 17 years?

Mr. SIEGEL. I think that SEDASYS is an excellent device and an important medical advance. It did raise important questions because in a sense, it is replacing the use of anesthesiologists in some cases, or at least it had the potential to replace use of anesthesiologists with a technology-guided approach to delivering anesthesia and ensuring that the patient is safely monitored. And that I think raised a lot of safety questions with the FDA. So I think the FDA had some legitimate concerns. I think it would be fair to say that there were times in the process where those could have been handled, communicated better, handled a bit more expeditiously so that the process would not have drawn out as long as it did.

Mr. BURGESS. Well, the idea behind giving people a predictable pathway going through this process was largely because of the experience that your company had, and I hope FDASIA actually has dealt with that.

Time is short, but Ms. Stafford, let me ask you, you have it in your written testimony. You didn't get a chance to really get to it, but the sharing of precompetitive data, how is that working out? How is that approached? Can you give us some real world examples of how that works?

Ms. STAFFORD. Thank you. It is a very good question. In terms of the precompetitive data, it is having access to electronic health records so that we are able to take that data and de-identify it. We don't want to know who the patients are, but we want to know how to find the physicians who have those patients and enroll them. The biggest time driver in this process when we talk about these 7 to 10 years of development is actually finding the patients. And when we talk about why do we go outside the U.S., it is partly to find the patients in a time frame in order to be able to get these products to market.

And so the precompetitive, if you will, data is really having access to data to help us find the right patients for the right trials in as rapid a time as possible. Right now on average, you know, anywhere from 10 months to 4 years, and, you know, there have been trials that have been put together, and there has been some proposals put forward and the ability to use data and to recruit the patients into a trial in 14 days. And just think about the amount of time that would be cut out of the trial from 4 years to finding patients down to 14 days because we have the data that gives us access to identify the patients.

Mr. BURGESS. Mr. Chairman, I have additional questions, and I would ask unanimous consent to be able to submit those for the record. I will yield back.

Mr. PITTS. All right. The Chair thanks the gentleman. I now recognize the gentlelady from California, Ms. Capps, for 5 minutes of questioning.

Mrs. CAPPS. Thank you, Mr. Chairman. And I thank you all for your testimony today. You know, providers and patients alike are relying on clinical trial data to ensure that we are getting the right treatment at the right doses at the right time. However, for too long these trials have not necessarily been representative of the population at large. And, Dr. Kesselheim, I have a couple questions

to ask you about this, but I wanted to just highlight where I am going with my questions. Women have been excluded, assuming that women are "men with hormones." Even lab rats in the past have all been male, and recent past. And diverse ethnicities have been underrepresented. And even when these groups are included in trials, often there are too few participants in these groups to analyze the effects on them or the analysis are simply not run or reported. More and more we are hearing about how disease manifestations can diverge based on gender. Recently there was a 60 Minutes story examining how some drugs affect women and men differently.

The story highlighted an example of the drug Ambien which metabolizes differently in women than men. Because of this, women have been unsuspectingly receiving high doses of the drug for over 20 years. This FDA change was followed by a report entitled Sex-Specific Medical Research, Why Women's Health Can't Wait, which provides compelling evidence for the further inclusion of sex and gender in scientific research.

And the FDA's own August 2013 report, which was initiated by the inclusion of my Heart For Women Act in the FDASIA legislation, shows that there is still much work to be done to make sure that women are fully represented in clinical trials and that the safety and effectiveness of information is readily available.

And to you now, Dr. Kesselheim, Brigham and Women's has been a leader in research on sex differences of disease. Can you tell us more specifically about the importance of ensuring proper analysis of drugs and devices on a diverse population? And what more can NIH, FDA, and private companies do to ensure that we don't have another Ambien situation?

Mr. KESSELHEIM. Thank you very much for bringing that up. I think it is a really important point, and I think the essential issue that your question goes to is the generalizability of the study and for a clinical trial for a newly approved drug or device to be truly generalizable, which is to say useful in the patients in which the drug will be used after approval, it needs to have representation of both sexes, people of different minority groups, without relation to their financial status or their sexual orientation or any kinds of things. The problem is, is that as we move in this conversation towards talking about more efficient trial designs and other kinds of processes to try to shrink the premarket study, what that inherently does is it reduces the number of patients in which a drug or device is tested in and so makes it even harder to achieve the kinds of goals that you are talking about and that have been recognized as being a problem in medical device trials of women underrepresented in device in trials of cardiovascular devices or in trials of new drugs that will then be used in those patient populations.

It is the same for older patients, and it is the same for younger patients. I think that Congress, just as it can put, encouraged the FDA to take up, you know, innovative clinical trial designs, can also encourage the FDA to make sure that the trials that are being delivered to it are fully representative of the patient population in which the drug or device will be used.

Mrs. CAPPS. Great. And I want to get another topic in real quickly for you because your written testimony also touches on the Sen-

tinel system under development by the FDA to conduct postmarket passive surveillance of drugs and devices to spot issues like adverse drug interactions quicker. And I believe that the Sentinel program holds great promise. That is why I worked to get the Assurance for Effective Devices Act included in FDASIA to continue progress on the program and ensure it would be designed for drugs and devices. So can you discuss—there is only a little time left—how the Sentinel program could be complement to the data derived from premarket clinical trials?

Mr. KESSELHEIM. Well, the Sentinel Initiative as you describe is a very promising pathway to try to get signals of safety issues for newly approved drugs and soon devices as well after they are approved. The problem is that the essential work in the Sentinel system of distinguishing the signal of the safety event from the noise of everything else that is going on with the drug in this post-approval observational setting is really very, very hard. So in the last 6 or 7 years, the Sentinel Initiative has been focused on the methods used to try to do this and has made relatively slow, steady, little progress, but steady progress, in trying to assess these kinds of methods.

There is still much, much more to be done before we can rely on the Sentinel Initiative for any sort of real active surveillance, and I think that that is far in the future, but unfortunately at this point my understanding is that the funding of the Sentinel Initiative is still up in the air, so I would encourage Congress to continue to fund it. But I would also not get people's hopes up that the Sentinel system is going to provide this great white knight from a post market surveillance point of view for drugs that are approved on the basis of limited pre-market study. I think the FDA itself still refers to the Sentinel Initiative as the mini Sentinel pilot program now 6 or 7 years out from its creation.

Mr. PITTS. The Chair thanks the gentlelady. I now recognize Dr. Murphy from Pennsylvania for 5 minutes of questioning.

Mr. MURPHY. Thank you. I want to ask particularly about a couple of the issues related to psychiatric drugs. Certainly, many medications you have brought up with regard to some recommendations for advancing the speed of these are important, but in particular, with 60 million Americans affected in some level with psychiatric illness, 10 or 11 million with severe psychiatric illness, and about 3.6 million who are not in treatment in part because of whatever the reason be with medication, et cetera. Would there be some change in the recommendations you would make to advance or speed up research with regard to psychotropic drugs, and I will open that question to anybody. Nobody has any? Go ahead.

Mr. MEYER. Yes, I will at least try to touch on that. I agree that it is an area of great unmet medical need. I think the problem has been a couple of fundamental issues. One is how poor some of the neuroscience is in predicting targets that are amenable to becoming drugs, or targets for drugs. The second, though, is that these trials are exceedingly difficult to conduct, and, in fact, if one looks at drugs for antipsychotics and/or depression, even very well-conducted clinical trials often fail for effective drugs. So it is probably one of the more problematic areas to think about new paradigms of drug evaluation at the current time. I do think where the hope

is for the future is really a better fundamental understanding of neurobiology to identify true opportunities for targets.

Mr. MURPHY. Let me add to that. Ms. Stafford, you also mentioned I think in your written testimony about issues involving, we should be looking at some of the EU standards, and perhaps that would help expedite. I know right now part of the discussion is also in terms of TTIP in looking at this Transatlantic Trade Agreement, and those standards, I believe, should become part of that. Do you have any insights for us that you can provide with regard to some of the differences between the American FDA and the EU standards for advancing clinical research?

Ms. STAFFORD. Yes. I was specifically talking about the adaptive licensing pilot that was started in March, April of this year, so it is early stages in terms of Europe. And, you know, the FDA is having that discussion as well, so I don't think that they are too far behind, but I think encouragement to also pilot, there are a lot of different terms for this, progressive authorization, adaptive licensing, et cetera, and so, you know, that is the one major area that I was speaking to.

Mr. MURPHY. Thank you. I also have a question with regard to the HIPAA laws and how the interpretation of those may interfere. I know some other members asked questions on this, but I also have some further comments of this, of how perhaps there are some barriers in what HIPAA laws are preventing us from getting information that would be extremely valuable in advancing research. I would open that up to anybody if anybody would like to comment on changes. Dr. Siegel?

Mr. SIEGEL. I think since the time those laws were passed, we have had a lot of experience with them, and we have new types of information that can be collected in laboratories, and I think it is time for a relook. It is important that privacy be protected. I believe it can be done in ways that also facilitate the advancing of research. And I know that HHS actually had about 3 or 4 years ago an advance notice of public rulemaking that looked at both the IRB process for patient safety protection as well as the process for privacy protection. There is a lot of opportunity, I think, both to increase patient protections, while at the same time, allowing better availability of important medical information, whether it is minimal or no risk to patients.

Mr. MURPHY. Thank you. Dr. Herbst, do you have a comment on that?

Mr. HERBST. I guess one of the benefits of doing the genomics in the context of a clinical trial is then you actually have the informed consent from the patient. You are matching them to the therapy, and then you have their consent to do the discovery within the trial, hopefully identifying new targets for the future.

Mr. MURPHY. Do you think some of this is misinterpreted now by researchers or by physicians who are just afraid to go anywhere with it because of the HIPAA laws?

Mr. HERBST. I think people are concerned, appropriately so, and they file them, and you do have to look very carefully at what consent you have whenever you are asking a question with tissue. But, no, I think people are very aggressively trying to study what they

can, reconsent patients when they can also, so that we can match genomic markers to activity.

Mr. MURPHY. Thank you. Dr. Khosla.

Mr. KHOSLA. Yes. I just wanted to add when you talk about clinical trial networks and consortia, I think that is where the HIPAA laws may need to be modified, particularly in what Ms. Stafford was referring to in terms of kind of the pre-trial process. So before the subject has signed any consent forms, the electronic health record would need to be searched to identify participants at a given site. Currently that data can't leave that particular medical center to be merged into data from other centers.

So modifying that to allow that in a way that still protects patient privacy but allows for better ascertainment of potential participants at different sites would be very helpful.

Mr. MURPHY. Thank you. So the HIPAA laws as they stand, they were designed to help protect patients from exposure of confidentiality? They weren't designed to hamper research in other movements. I thank you very much. I yield back.

Mr. PITTS. The Chair thanks the gentleman. I now recognize the gentleman from Texas, Mr. Green, 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman, and Ranking Member Pallone and for our witnesses here today.

In a time of historic opportunity offered with big data and scientific advances and technological developments it is important to examine the ecosystem of clinical trials. Before us is the prospect of transitioning from reactive systems centered on large patient populations, large clinical trials, and one-size-fits-all approach to a proactive system, they can target smaller, specific patient populations, advance personalized medicine, and revolutionize the way we prevent, treat and cure disease.

Dr. Siegel, clinical trial development in the area of antibiotics has been increasingly difficult in recent years because of the FDA trial design requirements. For instance, FDA requirements at trial study infection sites in the body versus the deadly pathogens that cause these infections that make conducting trials in the United States near impossible in large part because of the small population associated with these illnesses. How important is it to trial design successful trials, is an FDA empowered to accept alternative trial requirements based upon the unique nature of the disease and the patient population? By the way, I am sharing this question from Congressman Gingrey and I who have legislation working on it. So is there something that we can do that would make it easier on the smaller populations?

Mr. SIEGEL. Well, clearly infectious diseases are a major medical problem and threat to our country because of the rapid emergence of resistance and of new infections and because industry efforts in this area have somewhat decreased, in part because of difficulties in pathways. But I think the issue before us is the pathways that have traditionally been used and the way these drugs have been studied is, in fact, to develop them rather broadly for use, broad spectrum antibiotics for use in large populations. And as your question presumes, what is needed is a better effort to focus on specific needs to develop drugs that can be used in specifically the populations that need them so that resistance is less likely to emerge,

and to have innovative pathways that will allow that to happen and allow there to be ample incentives for investment in developing those therapies. I do think that there have been both legislative and regulatory moves in recent years in that direction, and I think that that is very welcome to, in fact, ensure that there are both incentives and pathways for more targeted treatments of critical infectious diseases.

Mr. GREEN. Anyone else? Dr. Meyer.

Mr. MEYER. Yes, thank you. I have actually worked on this issue, published on this issue, and actually I would say that FDA has shown some movement. I think one of the quandaries for FDA, however, is if they accept a smaller data set on a limited population for, say, a particular infectious agent, they don't really control the practice of medicine, and the issue for them is if they are reasonably assured that it works in that population but they don't want it broadly used either because of poor antibiotic stewardship and/or uncertainties about its general efficacy and safety, they don't have a good means for doing that. So I think that is part of the consideration that might be thought through in terms of approaching antibiotic drug development especially.

Mr. GREEN. And I agree in the real world of practicing medicine, but the FDA can put restrictions and advisories and things like that, so physicians may not, you know, use that particular drug for things that may not be proven on the label, but I know they don't have that ability in all the doctor's offices.

So, Dr. Siegel, your testimony brings up the potential for continued recognition of surrogate end points by the FDA as having great promise for continued drug development in the United States. Over the past few hearings and roundtables, you have heard of the dire lack of new diagnostic tests for many of today's illnesses and conditions. As the adage goes, if you want to cure something, you first need to be able to identify what it is. Dr. Siegel, since such tests operate largely against predetermined end points, could early FDA recognition of diagnostic end points for the purpose of clinical trial design improve the efficiency and success of those clinical trials?

Mr. SIEGEL. First, I want to say on record that the FDA program for accelerated approval has been a tremendous success. There is a large number of drugs, especially in cancer and HIV infection, that have come to patients much sooner, a large number of effective drugs that have come to patients sooner and a large amount of increased investment in those areas. There have been cases, as has been pointed out, where subsequent studies have shown that those surrogate end points did not predict benefits.

That, in my mind, is the evidence of the success of the program, the ability to learn in the postmarking situation, and, in fact, we have found when you just look at the numbers and the implications of the drugs involved, the benefits of those programs have tremendously outweighed the risk, the downside suggesting that more use, even though it would incorporate more risk, would be appropriate.

Diagnostic tools are critical to do that, diagnostics to identify the right populations and as you indicate, to measure end points. The use of diagnostics have been limited. The technological advances in proteomics and genomics and informatics offered the powers of explosive use—Dr. Herbst referred to some of that use in Lung-

MAP—in all aspects of clinical trial designs. And I think that investment in research in that area and investment in ensuring that we know how to integrate in both the research process, the product development process, and the regulatory process, we know how to integrate the development and the regulation of diagnostics with drug products is important since historically they have been done by separate organizations or companies.

Mr. GREEN. Mr. Chairman, I know I am over time, and I appreciate it. This is such a great panel with so much information, if you all have responses to not only my questions but other ones, please share them with us. And I thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman, and I now recognize the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. I too appreciate you coming and have been in and out, but actually have been around in these little anterooms and stuff. But I want to start with Dr. Khosla. In your testimony you state, and I am just going to quote, "The current clinical trial model of placebo-controlled, randomized, double-blinded clinical trial may not be the most effective model, particularly for early phase studies." And then in the case of antibiotics, when you use—I am really struggling with this, and I have actually been looking on my phone for the Hippocratic oath and issues. So if you are using a double-blinded, placebo-controlled test, and you have someone, and I use the term "emergent condition," and they are, maybe because it is a test you are using a placebo, doesn't that really cause ethical problems and challenges?

Mr. KHOSLA. Yes. I think you raise a very important point, which is the use of placebos in trials where effective medical therapy exists, and I should clarify that there have been enormous changes over the years in what is allowable and ethical to use as a placebo. So historically, for virtually all diseases, there were randomized controlled-placebo trials. More and more in my own area of expertise, for example, in osteoporosis, where we now have effective drugs to prevent or treat osteoporosis, instead of a placebo, often there is a standard-of-care drug that is used, and the burden of proof is to show noninferiority or superiority to the current best treatment.

So that is a great point that you raise, and it is in the context of where there may or may not be effective alternative therapies available.

Mr. SHIMKUS. I am going through this because one of the statements, and this is a modernized version. I will prevent diseases whenever I can. Prevention is preferable to cure. I am to care adequately for the sick. And when we are in a system like that, obviously we are not if it is placebo.

Mr. SIEGEL. It is important to note that the use of placebo in a clinical trial doesn't mean that the patient is not receiving a treatment. For example, with a new cancer drug if there is already two drugs being given, and a new drug comes along, some patients may receive all three. The others may receive the first two, but also a placebo so that there can be blinding as to which treatment, but they are still getting fully standard treatment. Placebos can be very important in research but should not be equated with lack of treatment.

Mr. SHIMKUS. Seems like this started some comments, and so, Mr. Murray, please.

Mr. MURRAY. Yes. So medical devices, it is a very important moral and ethical question. And there are instances for breakthrough medical devices where there is not an existing therapy, and you do a surgical procedure, especially with an active device that is not turned on, so the person is not receiving therapy. That, I think, adds to the conundrum, if you will, and I think it becomes a major challenge that is unique for medical devices especially in those breakthrough areas where there is a treatment-resistant diseases with no other options.

Mr. SHIMKUS. So let me go back to Dr. Khosla real quick. As far as in this process that we just discussed, any other FDA reviews or reforms that you would suggest that would be helpful in this process?

Mr. KHOSLA. Well, I think it really comes on a case-by-case basis depending on the particular disease being studied because for certain diseases there are effective cures, and you are really looking for a drug that might be better or have fewer side effects, and in that case, clearly the use of a placebo isn't warranted. In other instances, there really isn't a good alternative and the standard of care may involve, you know, for example, just giving nutritional supplements like vitamin D or calcium. And in those instances using an active drug against that standard of care is appropriate. So it is a major ethical issue. It is something, though, that is very specific to each disease entity and the alternates that are available.

Mr. SHIMKUS. Great. Thanks. And for my final minute, let me go to Dr. Siegel, and you talked about proteomics, if I pronounced that right, and molecular diagnostics and genomic sequencing. So what do you believe Congress needs to do to address and ensure that the potential for, I guess the terminology is precision medicine can be realized by both developers and clinicians?

Mr. SIEGEL. I think the potential to utilize those technologies in the development of precision medication is critical. I don't know that there is a specific legislative need to change the rules or the way drugs are developed. I think that we have what we need in that regard. I do know, however, as we have seen with breakthrough therapies, that congressional attention to an issue, highlighting an issue, congressional exhortations, congressional direction of how Federal agencies invest and spend their money can have a big impact, and I think in those areas certainly enabling FDA and NIH to help enable those technologies and those developments could be very important.

Mr. SHIMKUS. Thank you. And I know, Chairman, you probably have asked and will mentioned that there will be opening record for questions. There may be follow-up questions based upon your response. We would solicit and then we would forward to you. If you would do that, Mr. Chairman, I would appreciate it.

Mr. PITTS. Yes, we will have follow-up questions. The Chair thanks the gentleman. Now I will recognize the gentlelady from Florida, Ms. Castor, for 5 minutes of questioning.

Ms. CASTOR. Thanks to the panel for sharing your insights today. Dr. Meyer, I know you were formerly at the FDA and you have worked in industry, so I would like to get your insights based on

that experience on a couple of questions. We have heard a lot today about various ways that clinical trials can be modernized, everything from increased use of technologies like electronic health records to increased use of alternative trial designs like surrogate end points and adaptive trial designs. A lot of what has been mentioned I would assume is outside the purview of FDA. I imagine a lot goes on in the development of drugs and devices that doesn't and shouldn't involve FDA at all. I would like to hear your view on that. Do we have the right balance for the modern era?

Mr. MEYER. So I think some of what we have been hearing is outside the purview of FDA. For instance, the use of electronic health records for precompetitive screening of patients and understanding who the patient populations might be. That really is preregulatory as well. I think the expansion of the use of surrogates is clearly within the FDA's purview. I think the difficulty there, though, is not with the FDA. It is really identifying biomarkers or other assays that will be validated to predict outcomes. That is no easy task, and it sometimes takes a very, very long time. If you take for instance, Alzheimer's disease, everybody would like to be able to do much smaller, much more focused trials, but to date, the biomarkers we have have not predicted benefit. So there is no choice but to do large, long trials.

I think the other thing that I would say is that the FDA does, I think at times, have some reluctance to accept things like a patient-based electronic assessments. And I think that is something that they could be encouraged to do. I am not sure it needs legislation, but for instance, if you are a pulmonary patient and you are able to have a very reliable home spirometer and measure your air flow every single day, that is a very rich data source. But if FDA insists that those patients go into the clinic and be assessed in the clinic, that is actually inhibitory to patient enrollment to some degree, but also I think it produces a more expensive and complex trial.

Ms. CASTOR. Mr. Murray, do you think that the current regulatory scheme is meeting the entrepreneurial spirit that is out there? And I will give you a great example. In my home town of Tampa, we have a fantastic new center called the Center for Advanced Medical Learning and Simulation by the University of South Florida. I was so proud of it, I took Mr. Pallone to visit, and I know Mr. Bilirakis has been there where we are bringing together the medical engineers, the academics, the folks that can work through the business cycle, have the 3D printers right there so they take the device right to the 3D printer right into a computer analysis of whether it works or not. Does this regulatory scheme currently, is that going to be acceptable for the advances in technology and devices?

Mr. MURRAY. Excellent question. The genesis of MBIC was the recognition primarily from Dr. Jeff Shuren at CDRH and the commissioner that medical device technology is advancing at a rate that we have never seen before. You see it in the consumer and the mobile and the social media side, but you are seeing that translate over to health care as well. So there was a recognition that tools methods and approaches used needed to evolve, and to do that we are working collaboratively in the precompetitive space. And you

mentioned 3D printing. That is an example where you are going to see the realization of personalized medicine where using computational modeling and simulation, people will be able to have tailored custom devices that fit them and meet their needs specifically.

Where we are going right now, and I think the opportunity and the need, and we talked about this in terms of HIPAA and data, but there is a tremendous amount of data that is available out there in terms of patients' post approval of devices, and if you will, if you had the opportunity for, we have right now donor selections, if we had people that would be data donors instead of organ donors, and they would allow their data to be used, I think we could improve by orders of magnitude the quality and richness of those models and simulations to even improve more on the technology that is going to realize personalized medicine advancements.

Ms. CASTOR. Thank you very much.

Mr. PITTS. The Chair thanks the gentlelady. I now recognize the gentleman from New Jersey, Mr. Lance, for 5 minutes of questioning.

Mr. LANCE. Thank you very much, Chairman Pitts. In the various testimony of members of the panel, you have discussed the challenges in attempting to coordinate the work of multiple institutions before and during clinical trials. Varying regulations and protocols make it difficult, I think, for institutions to communicate one with another. If institutions that are attempting to coordinate have difficulty doing so, what about those that are not working together, and what methods are currently in place, if any, to reduce redundancies in clinical trials, and what steps would the panel recommend to ensure we are not doubling up on research or making the same mistakes over and over again. Dr. Siegel, yes.

Mr. SIEGEL. Well, there has been a lot of advances recently in terms of transparency of research results and rapid publication, and there has been a lot of growth of consortia, TranCelerate Pharma as an industry consortia, various other broader groups to enable better communication and cooperation. I think that you have heard from several members of the panel. One area, though, of better shared learning and cooperation that we see already but could see more of are disease-specific clinical trial networks and trials, such as Lung-MAP or organizations which bring together broad expertise. And one of the nice things about some of the newer approaches to that is that there are organizations that are not just, say, academic centers coming together with perhaps Government support, but are also incorporating patient and industry expertise and input to enable better addressing of some of the operational problems as well as the scientific problems that they need to face.

Mr. LANCE. Thank you. Dr. Herbst.

Mr. HERBST. Yes. I would agree with that. And just sharing our experience for the Lung-MAP trial, we are looking to accrue a thousand patients a year, and this is throughout the United States, really focused at the community, places that normally don't have access to these types of trials. So it really requires using the National Clinical Trials network, and that network uses a central IRB. We heard about that from the panel, so that this trial doesn't have to go through a different IRB at each site, which can take

weeks in some cases. So that is very helpful. I agree with Dr. Siegel, the commitment and working with all the partners, the Pharma partners especially, you know, the National Clinical Trials Network is being supplemented by the public-private partnership that we are working with. We need to all work together with the FDA as well because this would all be a failed effort if at the end of the day, these drugs and marketers couldn't go for approval of the drug. I think one thing we all have to also consider we heard a little bit about surrogate end points is quality of life and patient-reported outcomes and how we are going to build those into the trials and work with patient advocates and with those groups early on.

Mr. LANCE. Thank you. Yes, Doctor.

Mr. KHOSLA. I just wanted to reemphasize what I had mentioned in my testimony, which is that NIH is investing in these clinical translational science awards across the Nation, and so this is a pre-existing network where there are going to be best practices incorporated over time. There is hopefully going to be increasing IRB reciprocity, so many of the obstacles that we have heard about hopefully will be reduced or eliminated. And it isn't disease specific, so it would be open to any disease for which there is a trial ongoing.

Mr. LANCE. Thank you. To the panel, is there something more we should be doing here on this committee and at the Federal level to make sure that this occurs in the greatest way possible for the benefit of the better health of the American people? Yes, Dr. Herbst.

Mr. HERBST. Getting back to the whole idea of the public-private partnership, I think it is essential. In my, opinion that is one of the reasons the Lung-MAP is working well. Any way the committee could work to incentivize that to move forward the precompetitive measure. The fact that we have five different companies deciding to put their hat into our trial versus doing a trial themselves. I would hope that at the end of the day, they will see this is the only way to find these small populations of patients. But they are taking a risk, and ways to sort of incentivize, to promote, to give them credit for that, I think would be important.

Mr. LANCE. Thank you. Yes, sir?

Mr. MURRAY. And again, on public-private partnerships, but in particular with our partnership which includes NIH, CMS, FDA, the ability to have a flexible collaborative environment in that precompetitive space, it is oftentimes very structured—I think its FACA, if you will, that becomes an important consideration. So we have to be able to foster and encourage these kinds of partnerships in that precompetitive arena.

Mr. LANCE. Thank you. Yes, sir?

Mr. KESSELHEIM. Another thing that I would add is that I guess I am a little bit less optimistic than Dr. Siegel is about where things stand right now in terms of data transparency and the ability to share clinical trial data, and I think that this committee and Congress can do a lot to try to encourage and put in place systems and structures to allow sharing of clinical trial data to try to prevent redundancy in testing of new drugs and to try to allow different groups to learn from data that is currently right now held as a trade secret by many companies.

Mr. LANCE. Thank you. My time has expired, and it is been a very interesting and informative hearing. Thank you, Mr. Chairman.

Mr. PITTS. The Chair thanks the gentleman. I now recognize the gentleman from Louisiana, Dr. Cassidy, for 5 minutes of questioning.

Mr. CASSIDY. Dr. Siegel, the sharing of the data, it is proprietary data, so is the obstacle to the sharing the company releasing it? I am just asking.

Mr. SIEGEL. Obviously you need to have some protection of proprietary information in order for innovation to occur, in order to have incentives for innovation. However, when clinical trial data get to the point where what is learned about that data could be used to protect the safety of patients if it is a drug that is already approved or there——

Mr. CASSIDY. I accept that, but just in terms of expediting other research. I am just intrigued. Sounds like a great idea but will the companies agree to it? Do you follow what I am saying? I am not arguing either point. I am just asking.

Mr. SIEGEL. We have put in place through an agreement with Yale a third-party review that will enable much greater access to our clinical trial data where needed for important medical research in patient safety, and we believe that that is not incompatible at all with protecting innovation and allowing——

Mr. CASSIDY. I think it was the Michael J. Fox Foundation that, in order to receive their grant, you had to collaborate prior to peer review publication. Maybe I have that wrong, but nonetheless it seems like a nice concept. I don't know the practicality of NIH. Does NIH require that? I don't believe they do, do they? Anybody.

Mr. KESSELHEIM. I am not 100 percent sure. I would also support what Dr. Siegel has said about his company and its innovative relationship with Yale is actually quite a good model for other companies, but it is relatively rare at this point. I think that the NIH when it funds research, you know, should be held to the same standard as when companies fund research as well. But when research on products that are available in the market is done on patients, there is really no reason why that research shouldn't be available for further study and for greater learning by everybody.

Mr. CASSIDY. Dr. Herbst.

Mr. HERBST. I will just add that Yale and NCI Comprehensive Cancer Center, and I do know that the new regulations for recompleting those grants do require even more collaboration between centers, so hopefully through that we will bring the Pharma partners, too.

Mr. CASSIDY. Dr. Khosla, you and others mentioned having a centralized IRB, but that is already allowed. The Western IRB is the central IRB for many others. Now, would Mayo cede their—knowing how prestigious Mayo is, would they cede their IRB approval to a centralized western IRB, for example?

Mr. KHOSLA. I think the answer to that is that is a culture change that is occurring at many academic medical schools.

Mr. CASSIDY. So let me ask, that is merely a culture change. There is nothing regarding statute or regulation. I am asking because it seems like there is a certain institutional pride that some

institutions do not wish to cede. That truly seems more a culture issue than statute or regulation. Is that correct?

Mr. KHOSLA. Correct.

Mr. CASSIDY. Believe me, I am from that culture. I understand the hideboundness of it. Now, you also said something which I found intriguing. Dr. Herbst shook his head yes, that if you are doing the screening with genetic markers, that material, that information has to remain domiciled with the institution, and yet Southwest Oncology Group, I am just asking, you have multiple institutions. If one of them has certain biomarkers, they cannot share that with the centralized, whoever is overseeing the entire study framework. Whatever you learn cannot be shared with that centralized authority.

Mr. HERBST. Actually yes and no. First of all, the patient gets their data, so that is very important. So we are making this screening available to patients where they might not have had it or afforded it. And then, of course, the excess tissue does get banked through the cooperative group structure. That is not part of the national system.

Mr. CASSIDY. Now is that statute or legislation? Does that require an act of Congress? Oh, my gosh.

Mr. HERBST. No, no. The groups have tissue banks and the tissue goes in the tissue banks, and with petition anyone, it is a public bank, can petition the swag at some point if they have a study and they want to use this tissue.

Mr. CASSIDY. Dr. Khosla, I think what you said is that if you do biomarkers, those results remain at the institution and cannot be shared with others. Did I hear that correctly.

Mr. HERBST. No. Maybe you misheard me. This all goes centrally. In fact, the whole beauty of this is we are profiling at 500 different places with the same technique where it all goes through a central database. And that is the beauty of it. The point I was trying to make is we have very broad consent on these patients all very carefully through the IRB so that we are both putting patients on the drugs that we know now may or may not work. We are also able to discover new targets so the next four or five drugs that will come into the Lung-MAP we will be able to be more informed in what we choose.

Mr. KHOSLA. So just to clarify, what I was referring to was the preparatory to research phase so before the patient's actually been enrolled in the study to search the electronic health record, identify patients at a site, that information, before that patient has signed a consent form, can't leave that site.

Mr. CASSIDY. That is OK. I used to do clinical research, and I had 10 patients who I knew were interested in a trial. We knew from looking at their study. It is just that they had not had the formal testing. I don't see that as an impediment so much, and I forget if we did this. If it is illegal, I didn't do. But nonetheless, I would say listen, I have 10 patients whom I think we can enroll as soon as we start. There would be some sort of signal, knowing that it didn't guarantee, but it suggested it might happen. Is that an impediment?

Mr. KHOSLA. It is an impediment to the extent what when you have these national clinical trials networks, it is sort of an ongoing

process to recruit both a site investigator and the study participants. And so if you know up front where the patients are, then you can seek out individual investigators at those sites. So in that sense, it is an impediment.

Mr. CASSIDY. I yield back. Thank you for your generosity.

Mr. PITTS. Chair thanks the gentleman. I now recognize the gentleman from Virginia, Mr. Griffith, for 5 minutes for questioning.

Mr. GRIFFITH. Thank you, Mr. Chairman. I appreciate that. I am going to pick up on that real quick. There is a company out of Richmond that I have been real excited about. It is not in my district, but it is close enough. It is the The Health Diagnostic Laboratories, and what they do is do all the stuff on your blood looking mainly at heart disease and diabetes. I am sure they can add to their form a consent in advance, because what they are doing is tracking biomarkers and giving counseling to the people they have done the blood work on, obviously with the oversight of the physician. But they are giving counseling and trying to help folks avoid heart disease and diabetes, and a lot of times those biomarkers are overlapping.

And just seems to me that that might be a good place. Because they have got folks all over the country that they Fed Ex in their blood samples to and they—I call it they "Henry Forded" blood lab work. And it is really exciting stuff. And it just seems to me that might be something you all can look at and find a way, particularly if they get consent from their patients in advance, you might be able to track some of the biomarkers that you are looking for or some of the other things that you all are looking for that you then can get rid of that impediment that you were talking about by having a whole slew of folks automatically identified who may have already given advance consent at least to be contacted.

Ms. STAFFORD. I was going to say, I think the operative word is "consent." And as several of us have discussed, it is a matter of designing your consent up front that allows you that capability. And, you know, for instance, we have a tool, a technology, MediGuard.org where we have about almost 3 million patients that we have data, we have a relationship with. But we consent them, with them to participate in real world research with us, et cetera.

So I think it is about the consenting and what you put in that up front.

Mr. GRIFFITH. Absolutely. I would never want anybody's information being shared without their consent.

What do you find in your getting the consent up front? What do you find? It was about 5 or 10 percent that say they don't want their data being passed along?

Ms. STAFFORD. I don't have the metric. But it is interesting how many people want to be in the conversation. How many people are members of different, you know, groups like the ADA, American Diabetes Association or multiple sclerosis, and where they find their communities and how interested they are in research opportunities.

And so our database is really, you know, do you want us to communicate with you? Because they are all very interested in being part of research.

Mr. GRIFFITH. And you all mentioned it earlier in your testimony today that, you know, the technology and things are moving so much faster than it used to move, and it is exciting and really has great opportunities.

I want to switch gears a little bit, although it does connect. You know, I think about these issues of developing new treatments. And I have to tell you, I align with the mindset of those who support right-to-try laws that are being passed in the States. And I have introduced similar bills, two such similar bills here for patients whose doctors have exhausted current medical options, have been told that the end of life is nearing. My feeling is, why should the Federal Government interfere if the patient wishes to spend their own money on experimental treatment plans? I have this saying, if I'm dying anyway, why do I need to be protected by the FDA? Because death is near. And all treatment options have been tried.

That being said, I think the issue of benefit/risk framework should be brought forward in the earlier stages of a study of a new treatment by allowing an informed and responsible access to medications after the establishment of safety could allow for a faster translation of the science and technology from lab to clinic while insuring safety benefiting patients, and at the same time, leveraging our Nation's leadership and investment to advance science and technology.

One of the bills I have introduced, the Patient Choice Act, does this by creating a provisional approval process after drug safety has been established to allow patients to have access to new treatment while the efficacy is still being tested. This is similar to how things are moving in Europe.

I think this makes sense. I think it makes sense to empower a patient, as we have been talking about today, particularly faced with the dilemma of a terminal disease, to help move the ball down the field in the area of medical science and medical knowledge about fighting to save their own life with experimental drugs if they choose to do so. And even if they fail, the satisfaction of knowing that they may have helped save someone else's life.

So then the question comes, because I know that a number of you, particularly Dr. Meyer, are generally opposed to this kind of a concept. But when you are faced with the subset of that terminal patient, and their doctors have indicated that the current medical options have been exhausted, how do you tell that person that they can't spend their own money to try something that may not work but that might hold some promise? Dr. Meyer.

Mr. MEYER. So I would actually like to address that very point. Because actually from my experience at the FDA, it is usually not the regulators who are standing in the way of that. It is actually more often the companies. And there are a couple of considerations around that. Often they cannot charge, and going through the mechanisms to charge are very arduous. And they have to prove what their investments have been.

The other thing is that it ends up dirtying their data, if you will. So you mentioned the patient maybe having an altruistic view of even if I don't benefit, maybe others will. But unless they are in

a trial of some sort and their data collected in a rigorous fashion, they may not, in fact, contribute meaningful data to the evaluation.

So I very much am sympathetic to that view that those patients who have no other options, and there is a promising drug out there, should get access to it. But I think it really requires a thoughtful look at the ecosystem around that, if you will. And, you know, what is the problem, what is the fix.

Mr. GRIFFITH. Mr. Chairman, I know my time is up. I know Mr. Murray wants to respond as well. But I have to yield back at this point.

Mr. PITTS. Go ahead, Mr. Murray.

Mr. MURRAY. Thank you. I just would say patient choice we believe is an important aspect, and also the consideration for devices in that discussion. And to the extent that there are methods and methodologies to streamline how a patient may pay for a procedure, because that is a difficult aspect in this, especially if it is in a clinical trial, and how adverse data might be considered if it is not in a controlled environment.

Mr. PITTS. Chair thanks the gentleman.

Now recognizes the gentlelady, Mrs. Ellmers, from North Carolina, 5 minutes for questioning.

Mrs. ELLMERS. Thank you, Mr. Chairman. And thank you to our panel.

Ms. Stafford, I have the great honor and opportunity to be representing North Carolina and, certainly, your operation and organization there, the world headquarters right there in Durham. And I just have a couple questions for you. Again, obviously, our goal is to try to make the system work more efficiently so that we can get these very important drugs to market in a much quicker, efficient manner that is safe for all of our constituents.

My understanding, as we have learned about the clinical trial path that the sponsors who are collecting the data, they have to collect so many end points—I mean, dozens of end points—to demonstrate that the drug is safe and that it works. My question to you: In your opinion, how much data do we need, and are we collecting too much data? Is the data we are collecting truly efficient, or are we collecting so much data that it is just over in abundance? And can we find a process to narrow that down if that is the case?

Ms. STAFFORD. Thank you for your question. And of course, I am wearing my North Carolina blue, just to say.

Mrs. ELLMERS. Yes.

Ms. STAFFORD. Anyway, it is a very good question. And actually, I am a statistician by training. And I have seen in my almost 30 years in this industry now, we collect too much data. There is too much collected. And a lot of that comes from the multiple voices at the table.

And I do think that having the conversation up front, and I think the FDA wants to work with us on this with the industry. But there are a lot of key opinion leaders in the design of the trials, which includes many academic centers and scientists who have different opinions. And they want to prove that the drug is efficacious and safe, but they also want to explore what don't we know about the drug, what extra information can we get that is beyond really the investigation of that product.

Mrs. ELLMERS. Again, what I think you are saying here is, what we need to do is narrow the scope so that we can come up with the information. And certainly more information is great, and that can be used in many ways after the fact. But I agree. So would you say that up front, straightforward, more transparency and focus on the actual goals that are trying not to be put forward initially?

Ms. STAFFORD. Most panel members here talked about the trial design. And I think it all comes into the design and trying to focus the design. And, as you say, the scope and focus that scope and not enter into too much interesting extraneous data which end up taking time to collect the data. Once you have that data, what do you do with it?

Mrs. ELLMERS. Then you have to do something with it.

Ms. STAFFORD. It is just very costly, so trying to focus the scope of the trial design is my recommendation.

Mrs. ELLMERS. Very good. You know, there again, what we are faced with, or—we are seeing more of the trend toward global clinical trials. And, here for our committee, we are looking at ways that—we want to show incentives so that some of those clinical trials can be here and kept in the United States.

Can you make one or two suggestions on how we can achieve that goal so that we are doing more of those clinical trials or we are kind of returning back to a process where we are doing them here in the United States?

Ms. STAFFORD. I think we are having that discussion today in terms of ensuring that the U.S. is at the forefront of innovation around clinical trials. And that as long as we are the leader today in clinical research, we need to maintain that by being innovative and by modernizing the clinical trial and by being in a position to stay that leader. You know, drug development is no longer a one country, one continent, or one region. But we can certainly ensure that we keep our heritage as the clinical research leader by continuing this innovation discussion.

Mrs. ELLMERS. Thank you. And I saw some other nodding heads. Dr. Herbst, would you like to comment?

Mr. HERBST. Yes, I would agree. You know, I am a medical oncologist. Many of us who work in cancer have very busy clinics. There is limited infrastructure. You know, flat or declining public money. We are bringing some of the private money in. But really anything we can do to streamline the process, you know, the burden on the staff. You ask a few more questions, that means a coordinator or a nurse has to spend some time. You know, fewer, you know, rooms available. We want to put more patients on trial. Putting 5 percent of patients in this country on clinical trial is way too low. We have to do 20, 30, actually everyone should go on a trial in these incurable diseases, and to do that we really need as efficient as possible.

Mrs. ELLMERS. And, Dr. Khosla, do you agree with that?

Mr. KHOSLA. Yes.

Mrs. ELLMERS. Thank you.

Thank you, Mr. Chairman.

Mr. PITTS. Mr. Murray, you wanted to add something?

Ms. MURRAY. I would just state briefly for medical devices, the just-in-case perspective of what is going to be required at panel for

breakthrough devices and not knowing up front what a panel might ask. So bringing that part of the process forward would be very helpful. And also allowing for more flexibility in the early discovery. So when a new device comes out, you learn something in allowing for adaptive trial designs that incorporate and don't necessarily poison the data for the overall trial.

Mrs. ELLMERS. Thank you very much, Mr. Chairman, for extending my time a little bit there.

Mr. PITTS. Chair thanks the gentlelady.

Now recognize the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I appreciate it.

I want to thank the panel for their testimony today as well. And I appreciate you holding the hearing, Mr. Chairman. So very important.

Dr. Herbst, I am impressed with your multi-stakeholder partnership that resulted in the Lung-MAP program. Lung cancer has a 5-year survival rate of less than 20 percent. The work that NCI-designated cancer centers do is tremendous, as far as I am concerned. In the Tampa area, we have the Moffitt Cancer Center, as you know, which is the only NCI-designated cancer center in Florida. They have a partnership which has resulted in the Oncology Research Information Exchange Network, ORIEN. In my understanding, it is the world's largest clinically annotated cancer tissue repositories and data for more than 100,000 patients who have consented to the donation for research.

In your testimony—this is my question—in your testimony, you mention the importance of partnerships to accelerate clinical trials as well as the need to examine the incentives structure and process to facilitate data generation, sharing, and collaboration. Could you briefly elaborate on this and how this should be done, please. Can you elaborate?

Mr. HERBST. Right. And I do compliment Tampa on their work. They were one of the leaders initially in doing this personalized medicine network and bringing it together. And we are basically doing the same thing. The Lung-MAP is really, it is a truly national effort. And, as I mentioned, it came from an NCI panel and from work at the Friends-Brookings meeting.

And the thing that is very nice about it is, we are working closely with the FDA, with the foundation for the NIH, and others. We really want to really bring these drugs and this testing throughout the Nation to the community. So the idea basically is to pick and do profiling in one specific way at all the different centers. Within 10 days. You know, because patients can't wait, they have advanced disease. You are right. This is even worse than what you mentioned because this is squamous cell lung cancer, mostly a smoker's lung cancer, where there really are no other therapies to offer these patients. The most advanced, widespread disease.

And then we are randomizing patients to either the standard of care or to one of these new drugs based on the molecular profile. And we have five different drugs. So the way this has worked has really been a good concept, something that the academic community, the clinician community around the country, and the drug companies and the private payers see as a very important way to

move forward. And we have all worked together. And it has taken a large amount of collaboration, meetings. It really is a partnership. And I sit here now, but there are hundreds of people who have been involved in this process. And I am very proud of how we have all worked together. And we are doing it for the patients.

And the other thing that is very important is advocacy community has been involved with us from the very beginning. And they have advised us on some of the issues regarding disclosure and forms and consent forms. And we have really worked—this is really focused on the patient and bringing more drugs to patients quicker.

And I just want to add, the FDA has been so supportive of this process. Of course, these trials all have to go through the standard phase II, phase III criteria. In fact, they are very strict criteria. But we have had advice as we move along: How do you integrate the markets into the trial? So I would say this is something that has to be emulated. And other diseases are already working on this. There is a trial in colon cancer that is moving forward, breast cancer, and others as well.

Mr. BILIRAKIS. Terrific. Very encouraging. Thank you, Doctor.

Dr. Siegel, you raised the issue of providing greater voice for patients in clinical trials. You mentioned that the investigators only use objective outcome measures—the investigators, but not information from patients like, how did they feel, how are they progressing? How could investigators and regulators use qualitative data when making decisions?

Mr. SIEGEL. Well, thank you for that question. I think it is an important one. It is easier, I think, and that is probably why there is a history of using things that can objectively be measured in the lab or life or death. But beyond what the exception of life or death, usually what is most important is how a patient feels.

There is a science behind how to do that. If you are not careful about how you do that, you can introduce a lot of bias, you can use tools that mis-weigh and that don't really represent patient outcomes.

So that has been part of the reluctance to—or maybe the slowness in incorporating patient-reported outcomes. With that said, I think we are at a place where they can and should be incorporated much more broadly in almost all areas of clinical research.

Mr. BILIRAKIS. Thank you very much. Another question for you, Dr. Siegel. Can you explain in laymen's terms what adaptive clinical trials are, how they are different from traditional clinical trials, how has FDA viewed adaptive trials? I believe they have released guidance just a few years ago. And have adaptive trials been used in Europe? And what lessons can be learned from Europe?

I am not sure if that has been covered, because I had to step out. But if you could elaborate, I appreciate it.

Mr. SIEGEL. Not in any depth.

So more traditional trials, you design the trial and how you are going to conduct it and how you are going to analyze it up front. And then at the end, you unblind the data and you do your analyses.

That offers the advantage of avoiding a lot of biases that can lead to inaccurate assessments of treatment effects.

In adaptive trial designs, you learn as you move on. You use biomarkers or actual outcomes in patients, if they are available fast enough, to understand what are the more promising therapies, perhaps, maybe putting more patients onto those therapies, changing randomization, substituting changing or selecting among doses. Or even select changing entry criteria. You could change almost any part of a trial.

A lot of scientific work has gone into how to utilize adaptive trials, because if done wrong, there are opportunities to introduce bias. But they allow real-time learning from what is happening within a trial. Therefore, they can be extremely powerful tools in drug development.

The FDA has been out in a leadership position in terms of providing guidance as to how they could be used in the regulatory setting. There is, of course, some conservatism because of the scientific challenge.

But it is an opportunity to accelerate our ability as you have heard about from Dr. Herbst, to accelerate our ability to learn within clinical trials. And I think it is one that is very much underutilized.

Mr. BILIRAKIS. Very good. Thank you.

I yield back, Mr. Chairman.

Mr. PITTS. Chair thanks the gentleman.

That concludes the first round of questioning.

This has been another exciting, informative, important hearing. A lot of members have follow-up questions. So we will send those to you within 10 business days.

I remind members they have 10 business days to submit questions for the record. I ask the witnesses to please respond to questions promptly. Members should submit their questions by the close of business on Wednesday, July 23rd.

Without objection, subcommittee is adjourned.

[Whereupon, at 12:18 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Rep. Cathy McMorris Rodgers
Opening Statement
July 9, 2014
21st Century Cures: Modernizing Clinical Trials

Thank you, Mr. Chairman, for yielding to me.

I am happy to be here today to discuss how we can leverage new technologies with existing infrastructure to improve the way clinical trials are conducted in the U.S. By cutting down on administrative inefficiencies, creating a glide-path for the adoption and acceptance of new trial designs, and lowering the costs necessary to conduct a trial, we can get therapies to market faster and save lives as a result.

The goal of clinical trials is to demonstrate safety and effectiveness. The question is: can those qualities be demonstrated without three or four part trials, which cost millions of dollars and take six or seven years? I believe that this is well within our grasp.

Perhaps we can start with steps that simplify administrative procedures and what it takes to start a trial – such as standardizing IRBs and ensuring the creation and maintenance of "ready to go" clinical trials networks.

We can work with FDA on the type of evidence they require for approval – and what Congress can do, in collaboration with the agency and other stakeholders, to promote the use of innovative new tools in clinical trials – such as qualifying biomarkers and using surrogate endpoints to prove effectiveness. These steps, together with using other tools like big data and complex

modeling, can help us take clinical trials into the 21st century – by allowing us to yield better and faster results, with fewer people needed, less investment, and shorter approval times.

I look forward to working with the Chairman and committee on the overall Cures initiative and to advancing initiatives that improve the clinical trials system and ideas that will increase FDA's overall comfort and acceptance of new trial designs. I am confident this initiative will generate new kinds of evidence, expedite the clinical trials process, and create life-saving therapies for the American people.

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

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Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE

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July 29, 2014

Dr. Robert J. Meyer
Associate Professor
Public Health Sciences
University of Virginia
P.O. Box 800717
Charlottesville, VA 22908

Dear Dr. Meyer:

Thank you for appearing before the Subcommittee on Health on Wednesday, July 9, 2014, to testify at the hearing entitled "21st Century Cures: Modernizing Clinical Trials."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Tuesday, August 12, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

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Monday, August 11, 2014

Joseph R. Pitts.
Chairman, Subcommittee on Health
c/o Sydne Harwick, Legislative Clerk
Committee on Energy and Commerce,
U.S. House of Representatives
2125 Rayburn Office Building
Washington, DC 20515-6115

Dear Chairman Pitts.

I am pleased to be able to respond to the additional query which you sent in follow-up to my participation in the discussion of Modernizing Clinical Trials held on July 9th, 2014. Specifically, this query came from Representative Murphy on the issue of impediments to the development of innovative psychiatric drugs, which he and I agree is an area of substantial unmet need given the prevalence of mental health issues in the United States. Representative Murphy asked for me to provide expanded remarks "pertaining to the problems psychiatric drug developers face and for commentary on any potential changes that could be made to resolve this problem." While this therapeutic area was not a part of my direct responsibilities when I was an Office Director at FDA's Center for Drug Evaluation and Research, I did have a broad regulatory strategy and drug development role while at the Merck Research Labs and Merck's portfolio included many drugs targeting psychiatric diseases. I saw firsthand how many drugs in this area of development failed in the late stages of clinic development, if not before. I have also taken the liberty to discuss my response with subject matter experts within my former company to assure that my response represents current state and well-targeted.

As well stated at the July 9th hearing by Rep. Murphy, despite a large number of pharmacologic agents available to treat psychiatric diseases (such as depression, schizophrenia, bipolar disorder), there remains a large number of patients who are not adequately treated for their illnesses with a resultant substantial burden on society. While some of this burden may be the result of the availability of and access to proper psychiatric care, clearly a large part of this continuing problem is a less than satisfactory array of therapeutic options. Yet, while this unmet need is substantial, global pharmaceutical companies are decreasing investment and research in the area of psychiatric drug development[1], in part due to the burden of failures in their attempts to provide better options to patients. The article cited above by Dr. Hyman (former Director of the NIMH) is, in fact, a very

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good summary of some of the current challenges to this therapeutic area and aligns well to the discussions I had with other experts on some of the major impediments and issues with productivity in psychiatric drug development. I would recommend this article as a very thoughtful review.

However, let me highlight some key issues from my vantage point:

- While great advances have been made in the fundamental understanding of basic sciences and pathophysiology in a large number of human diseases, including neurology, this same kind of clear understanding of the fundamental basis of key psychiatric diseases has not been achieved (including what differentiates between the diseases/syndromes pathophysiologically). This lack of basic understanding is compounded by the lack of useful animal models for many psychiatric diseases, such as schizophrenia.[ii] To date, many advances in psychiatric drug therapy have come through serendipity rather than by design. In contradistinction to classical therapeutic science, these drugs' activities have driven the theory of disease rather than more usual and rational visa-versa. For instance, it was the association between the depletion of catecholamines (major neurotransmitters) by reserpine (a blood pressure medicine) and its frequent adverse effect of depression that led to the catecholamine hypothesis of depression – which remains controversial to this day, but has been the basis for much of the treatments developed for depression.

  Great advances in the fundamental understanding of the genomic basis of disease have been achieved for many disease areas, which in turn have informed targeted drug discovery and development. A great example of this kind of mechanistic drug development is ivacaftor for Cystic Fibrosis.[iii] Yet, the genetics of psychiatric diseases have proven to be exceedingly complex, despite clear heritability (particularly schizophrenia, where genetics are believed to account for 50 – 80% of the disease risk). The complex, multigenic bases of these diseases have not led to a rational set of targets for further drug discovery.[iv] That is not to imply important advances have not been made, but clearly more understanding of the genetics, epigenetics, and other underlying pathophysiologic basis of psychiatric disorders is sorely needed in order to inform more rational drug development. This is a need best served by academic and/or governmental basic science researchers, rather than drug companies, as it involves fundamental, rather than targeted, science. Continued or enhanced government support of this kind of basic research in academia would be an important consideration for advancing this area of drug discovery.

- A second need as an underpinning of translational efforts in neuropsychiatry is the development of predictive biomarkers, not only to better identify patients at risk (which may be particularly important for enrichment and enhanced success rates of clinical trials) but also to inform proof-of-principle studies in very early clinical development. The use of biomarkers in early drug development is particularly important as predictive biomarkers

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provide a means to screen compounds for likely clinical efficacy long before large investments of time and dollars are committed to the drug's development. Currently, few such biomarkers exist for psychiatric disease states. Public investments in furthering efforts to identify and validate biomarkers in psychiatry for the purposes of better identifying patients at risk as well as informing drug choice and development is clearly needed.[v] This kind of research is being done and should continue to be done both in academia/NIH, as well as within the industry itself, and directed support of public/private partnerships with this specific mission would be worthy of consideration.

- As for clinical trials, there are a variety of issues that may be impacting the relatively low success rate for psychiatry drugs entering into phase 3 (many of which fail for efficacy). These factors include:

    - Highly variable diseases (where the "placebo effect" may be substantial, due in part to "regression to the mean" in patients who are enrolled for a certain high level of disease symptomatology)
    - Imprecision in enrollment criteria due to lack of definitive, differentiating diagnostic criteria, compounded by a lack of characterizing biomarkers for disease state/activity
    - Imprecision of current clinical trials endpoints, much of which are based on questionnaires and subjective assessment tools, rather than a measurable physiologic parameter or other objective measures
    - The need to provide evidence to payers and practitioners of therapeutic superiority over existing drugs, most of which are generic (this complicates the design of the trials, but even for well-designed trials this sets a high bar for efficacy and/or safety)

Addressing the unmet psychiatric need through novel drug development requires advances in a number of areas, including the basic sciences of psychiatric diseases. Some of these factors could be improved if the issues highlighted above were successfully addressed (e.g., fundamental discovery science and development of biomarkers). However, like many areas of drug development/clinical testing, the reduction of inefficiencies in trial design/conduct and factors that add noise to the trial results (particularly the imprecise or indiscriminate inclusion of patients) is also needed. This is largely the purview of the industry itself and correctly so. That said, as in many areas, having standing networks of high quality clinical trial sites that can rapidly recruit well-characterized, appropriate patients to new trials would be advantageous. Since one would want sophisticated screening and enrollment of patients, any such networks should include academic medical centers as key contributors. The establishment of funded, standing networks would reduce factors that add to the substantially to the costs of drug development (irrespective of failure rates), such as site identification, patient identification, IRB clearance, etc.

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A final thought on the industry's pull back from investment in this disease area: in counter distinction to an area of drug development like antibiotics, one thing that does not seem to be a factor in the dwindling R&D efforts is economic reward. While most important psychiatric drugs are now off patent, recent history in the industry shows that this area of drug development, when successful, has led to high revenues during the drug's exclusivity. Indeed, if one were to be able to understand sufficiently the basic causes of a condition like the cognitive impairment in schizophrenia (which is not at all addressed by current anti-psychotics), a successful program addressing this need would surely result in a sizeable market/revenue opportunity.

The issues behind the low productivity for meaningful therapeutic advances in psychiatric therapeutics are daunting and deep. However, as I stated in the hearing itself, I do not believe the fix to these issues relates to developing accelerated pathways to approval, since the fundamental sciences remain inadequate and, in particular, we do not have sufficient surrogate endpoints that would form the basis for being able to speed development (let alone improve clinical success rates). What is needed is to bring our considerable and potent tools of scientific discovery to bear in a cohesive, coherent effort to systematically advance the fundamental understanding of psychiatric disorders in terms of biologic causes and the pathophysiologic distinctions between the diseases. Only through such understanding will there come to pass a more informed, targeted and rational development of new therapeutics with a resulting increase in the chance of clinical success that is so very necessary to address the large remaining unmet medical needs in this vexing area of medicine.

Sincerely,

[redacted]

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[i] Hyman, Stephen. Psychiatric Drug Development: Diagnosing a Crisis. *Cerebrum* (April 2013) [http://www.dana.org/cerebrum/2013/psychiatric_drug_development__diagnosing_a_crisis/]

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[iii] http://www.cff.org/treatments/therapies/kalydeco/

[iv] Ozomaro, et al. Personalized Medicine in Psychiatry: Problems and Promises. BMC Medicine (2013); 11:132

[v] Wiedermann. Biomarkers in Development of Psychotropic Drugs. Dialogues Clin Neurosci (2011); 13:225-234

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July 29, 2014

Dr. Jay P. Siegel
Chief Biotechnology Officer and
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Dear Dr. Siegel:

Thank you for appearing before the Subcommittee on Health on Wednesday, July 9, 2014, to testify at the hearing entitled "21st Century Cures: Modernizing Clinical Trials."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

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Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

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Johnson & Johnson

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August 18, 2014

The Honorable John Shimkus
Energy & Commerce Committee
2452 Rayburn House Office Building
Washington, DC 20515

Dear Representative Shimkus:

Thank you for the opportunity to provide additional information regarding the Subcommittee on Health hearing entitled, "21st Century Cures: Modernizing Clinical Trials."

1. You state in your testimony that "advances in next generation sequencing, imaging and molecular diagnostics (e.g. proteomics) are contributing to our understanding of how and why drugs may have different effects in different individuals with the same diagnosis." In what ways can such genomic sequencing and molecular diagnostics help support subpopulation drug and device development?

Advances in next generation sequencing, imaging and molecular diagnostics enable us to study, in greater detail, a disease process and the response to therapy in individual patients. When these advanced tools are used to study populations with what appears clinically to be the same disease, they often allow recognition of different subpopulations of patients with somewhat different disease processes at the molecular and cellular level. This testing and recognition can lead to the discovery of drugs specific for a subpopulation (i.e., targeted therapy), and facilitate the clinical testing of targeted therapeutics.

With regard to discovery, when a pathophysiologic process is found to be prominent in a subpopulation of patients, one has a clue that targeting that process may lead to discovery of a valuable intervention.

In clinical trials, use of biomarkers and imaging agents enables one to identify and study patients with the specific process being targeted. A study focused on those patients most likely to benefit or least likely to be harmed is more likely to be beneficial to participants, has increased probability of success, and, in some cases will have lower costs and shorter timelines. When a drug's use is limited to the population most likely to benefit and/or least likely to be harmed, the risk-benefit profile will likely be far better than when it is used more broadly.

Several innovative clinical research designs have been developed to make use of biomarkers and imaging modalities in clinical research. For example, a broad collaboration between FDA, industry, not-for-profits, and academic researchers has developed Lung-MAP, a master protocol for studying several drugs in advanced squamous cell lung cancers. In this study, use of biomarkers in patient screening informs treatment choices for initial patients, and learning from the ongoing trial about which patients respond best to which treatments informs treatment choices for subsequent patients. The goal is a more cost-effective and efficient process for identifying effective treatments.

2. What types of barriers do you believe Congress needs to address to ensure that the potential of precision medicine can be realized by both developers and clinicians?

I mentioned a number of barriers to realizing the potential of precision medicine in my testimony. First, electronic health records (eHRs) have enormous potential to inform clinical care. For precision medicine, eHR registries of patients could serve as a critical tool to identify subpopulations and target their treatments, particularly if the eHRs included, or were supplemented with, patients' genomic, proteomic, and imaging profiles. However, significant barriers to such use include the lack of standardization and quality control for eHRs, lack of interoperability of her systems, needed development of methodology re eHR data use, and the need for educating clinicians on the value of eHRs and incentivizing their use. Additionally, the process for obtaining consent and approvals for use of de-identified eHR patient data with minimal or no risk to the patient could be simplified while maintaining protection of privacy and rights.

Second, clinical trial networks created and governed by broad consortia, as mentioned in the response to question 1, can be a very valuable tool for clinical research in precision medicine. However, the numbers and reach of such consortia and networks are limited. Government, especially FDA and NIH, can play an important partnership role in creating and governing such networks; Congress should encourage and support those efforts. Patients, academics, and companies also will bring important insights and capabilities.

Third, a barrier to including a large, diverse, broadly representative group of patients in clinical trials is the lack of public education about the value of participation in clinical research while dispelling common misperceptions.

Three additional areas that would benefit from Congressional attention to aid in the realization of the potential for precision medicine are described below:

1. FDA has made progress in improving its coordination and internal collaboration in the regulation of targeted therapeutic agents with diagnostic tests, but more needs to be done. We suggest that Congress continue to encourage FDA's development of a consistent, efficient, transparent and coordinated regulatory pathway for these products.

2. With advances in the science behind precision medicine, the use of a diagnostic that optimizes the use of a drug in a subpopulation is quickly becoming a key tool in patient therapy. Current reimbursement policies for novel diagnostics that are used in precision medicine do not reflect the potential benefit they can bring to patients and the healthcare system. Congressional attention could help ensure appropriate reimbursement and market access.

3. Full realization of the potential of precision medicine will require continued and robust scientific innovation, and we would welcome Congressional actions to increase incentives for innovation that advances precision medicine.

Thank you for your consideration.

Sincerely,

ANDREA MASCIALE

Digitally signed by ANDREA MASCIALE
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Reason: I agree to the/affect the/form of this document
Date: 2014.08.18 13:24:23 -04'00'

On behalf of

Jay P. Siegel
Chief Biotechnology Officer
Head of Scientific Strategy and Policy

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
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WASHINGTON, DC 20515–6115
Majority (202) 225-2927
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July 29, 2014

Dr. Sundeep Khosla
Director
Center for Clinical and Translational Science
Mayo Clinic
200 First Street, S.W.
Rochester, MN 55905

Dear Dr. Khosla:

Thank you for appearing before the Subcommittee on Health on Wednesday, July 9, 2014, to testify at the hearing entitled "21st Century Cures: Modernizing Clinical Trials."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Tuesday, August 12, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905

August 12, 2014

The Honorable Joseph Pitts
Chairman, Energy and Commerce Committee
Subcommittee on Health
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pitts,

Thank you for the opportunity to testify at the Committee on Energy and Commerce "21st Century Cures: Modernizing Clinical Trials" hearing on Wednesday, July 9, 2014.

At your request, attached is my response to the additional question for the record posed by Representative John Shimkus.

Sincerely,

[redacted]

Sundeep Khosla, M.D.
Dr. Francis Chucker and Nathan Landow Research Professor
Distinguished Mayo Investigator
Director, Mayo Clinic CTSA/Center for Clinical and Translational Science
Dean for Clinical and Translational Science
Mayo Clinic

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health
The Honorable John Shimkus, Member, Energy and Commerce Committee

(1) The Honorable John Shimkus

(2) You state in your testimony that "the current clinical trial model of placebo-controlled, randomized, double-blinded clinical trial may not be the most effective model, particularly for early phase studies." In the case of antibiotics, for instance, a placebo-controlled randomized, double-blinded trial would require a patient in an emergency room seeking treatment for a deadly disease to be unaware that they are not receiving treatment. Is that a fairly accurate statement?

From an ethical standpoint, I have trouble squaring that placebo-controlled double blinds are always the best method of study—especially when a patient is suffering life or death consequences from such requirements. Have such FDA requirements forced researchers and developers overseas to conduct such trials and do you believe reforms in this area might help encourage greater research opportunities?

(3) Thank you for this very important question. I should clarify that the statement in my testimony regarding placebo-controlled trials assumed that "placebo" represented appropriate, standard of care for the disease in question. Unfortunately, I did not make this clear. Thus, in the example you provided, no Institutional Review Board (IRB) in the United States (or I believe anywhere) would permit a study to be conducted where patients were denied appropriate treatment (e.g., antibiotics). For the specific situation you mentioned, the "placebo" (or more appropriately, the "control") group would receive standard antibiotic therapy consistent with current practice, whereas the treatment group would receive the new antibiotic. In that instance, the question would be whether the new antibiotic is superior, or non-inferior, to standard therapy.

This issue is dealt with on a case-by-case basis. In the situation where no effective treatment for a condition is available, then a true placebo may be justified, as that represents standard of care. Thus, the issue of the use of placebos is one that is carefully considered both by investigators and by IRBs. While advancing medical knowledge and finding new cures is clearly important, paramount in the minds of all clinical trial researchers is the safety and appropriate care of all patients.